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PNEUMONITIS ASSOCIATED WITH MALARIA

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Infections of the respiratory tract associated with malaria, recognized for many years, offer a wide scope of interesting and controversial aspects. While foreign literature has contributed sporadic studies, American publications have been few.

Meersseman [1] in a critical study of pleuropulmonary manifestations of malaria presented a historical background for the subject. He stated that Grosset reported the first detailed study of the disease in 1783. Previously there were only occasional references. He alluded to the contributions of Broussois in 1822, Heschl in 1850, J. Frank in 1857 and such military surgeons as Jacquet and Frison. Hamelin in 1896 presented a thesis based on the observation of 3 cases of pneumonia which he considered to be due directly to the plasmodium of malaria. In a series of publications between 1892 and 1902 Laveran contested the view that pneumonia was due to the parasite per se and suggested instead that the lesion was a superimposed infection. However, Traite in 1910 took a firm stand in favor of the existence of the disease malarial pneumonia. Meersseman also included the study of Tricoire, who in 1924 presented 2 cases of malarial pneumonia with hemoptysis as the presenting symptom. Studies of the sputum in both cases revealed the plasmodium, and in 1 case the parasite was recovered by lung puncture. One of the most interesting reports in this historical sketch was by Zimine, who in 1936 detected quartan malarial parasites in a case of hemorrhagic pleural effusion, which responded promptly to quinine.

An interesting classification, based on clinical observation, was formulated in 1932 by Mouradian,[2] who divided the acute respiratory forms of malaria into: (1) bronchitis; (2) the grippal form with frequent pulmonary congestion, and (3) the recurrent grippal form. He believed that the bases of the lungs were most frequently involved and then the midzones. He warned that lesions of the upper lobes must not be confused with pulmonary tuberculosis, although this possibility had to be ruled out.

Disturbances of respiratory function in malaria had been studied by Meldolesi,[3] who in a survey of 30 cases noted a deficiency of arterial oxygen by means of investigations of the blood. He concluded that this finding was more common in estivoautumnal malaria and in the quartan type than in the tertian form. Anoxemic disturbances were consequential, and acidosis was another finding.

Strong,[4] in Stitt's textbook of tropical medicine, briefly referred to the pulmonary form, which has an element of periodicity and responds to quinine. Nocht and Mayer [5] mentioned the pneumonic form of malaria, in which hemoptysis is an outstanding symptom and is attributable to the parasites' filling the blood corpuscles of the pulmonary capillaries. Castellani and Chalmers [6] stated that whether or not there is a malarial pneumonia is a vexed question. They believe that severe estivoautumnal malaria may produce a symptom complex resembling pneumonia but that a true lobar pneumonia is merely a complication of bacterial origin. In the "Oxford Medicine" [7] the occurrence of bronchitis, pleurisy and pneumonia in malaria is recorded. The rarity with which the parasites are detected in the sputum and the occasional finding of small hemorrhages in the lungs also are noted.

Among the more recent publications dealing with respiratory diseases in malaria are the contributions of Oropeza T., [8] Epure,[9] Guseyn-

From the Medical Service of Gorgas Hospital, Ancon, Panama Canal Zone.

1. Meersseman, F.: Pleuropulmonary Complications of Malaria: Critical Study, Progrès méd., May 1, 1937, pp. 666-670.

2. Mouradian, H.: Bronchopneumopathies in Malaria, Paris méd. **1**:349-358 (April 23) 1932.

3. Meldolesi, G.: Respiratory Disorders in Malaria, Boll. e atti d.r.Accad.med.di Roma **57**:310-316(Oct.) 1931.

4. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1942, p. 73.

5. Nocht, B., and Mayer, M.: Malaria, London, John Bale, Sons & Curnow, Ltd., 1937, p. 15.

6. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, New York, William Wood & Company, 1913, p. 889.

7. Christian, H. A.: Oxford Medicine, London, Oxford University Press, 1942, vol. 3, p. 785.

8. Oropeza, T. J.: Bronchopulmonary Complications of Malaria, Rev. de med., Rosario **2**:291-295 (May) 1927.

(Footnotes continued on next page)

Zade,[10] López,[11] Spencer,[12] Fauci,[13] Abbasov,[14] Calò,[15] Mailyan [16] and Padoan and Corseri.[17] No significant conclusions were noted, and many articles were merely case reports. In 1943 Campbell [18] concluded the study of 50 patients in the Panama area and believed that all had atypical pneumonia associated with malaria, running the usual course, unaffected by the combination of the two diseases.

Patients with pneumonia associated with malaria were frequently encountered at Gorgas Hospital and constitute the basis of observation and study in an attempt to clarify this problem.

METHOD AND MATERIAL

One hundred and twenty-five consecutive patients with pneumonia associated with malaria admitted to Gorgas Hospital during the seventeen month period from January 1942 through May 1943 were selected for study. Each patient received the routine admission hospital work-up, consisting of taking of the history, physical examination and laboratory procedures, including a complete and differential blood cell count, determination of hemoglobin, serologic tests of the blood, urinalysis, examination of the stools and studies of thin and thick blood films for malaria. The examinations of blood films for malaria were repeated daily until there were several successive negative results. Roentgenologic studies were performed in over 97 per cent of the cases, and serial follow-up films were taken in the majority. Specimens of sputum were investigated in about half of the cases. Other laboratory methods were employed for purposes of differential diagnosis.

A study of the type of patients, incidence, seasonal occurrence, symptoms, objective findings, results of roentgen examination, laboratory data, response to therapy, course and complications was made on the entire group.

RESULTS

Type of Patient.—Most of the patients were young white men attached to the military personnel. The next largest group consisted of young Negro men employed on the Panama Canal. The following tabulation is a record of age, sex, race and occupation for the entire group:

		No. of Patients	Percentage
A.	Age (years)		
	1. Birth to 13..... (Infancy and childhood)	7	5.6
	2. 14 to 40..... (Adolescence and adult)	111	88.8
	3. 41 to 60..... (Middle age)	7	5.6
	4. 61 and over..... (Older group)	0	0.0
	5. Youngest, 1 year Oldest 51 years		
	6. Average—27.4 years		
B.	Sex		
	1. Male	118	94.4
	2. Female	7	5.6
C.	Race		
	1. White	98	78.4
	2. Negro	18	14.4
	3. Foreign white (white persons not U. S. citizens)....	9	7.2
D.	Occupation		
	1. Military personnel.....	87	69.6
	2. Canal Zone employees.....	29	23.2
	3. None	9	7.2

Incidence and Seasonal Occurrence.—The incidence of pneumonitis in persons with malaria in the military group was 3.7 per cent. The occurrence was greatest during the rainy season (May to December), when both malaria and primary pneumonitis were most frequently encountered as separate entities. The following outline furnishes more detailed data:

A. Relationship to uncomplicated malaria and pneumonitis in a similar period (entire year of 1942)
   1. The incidence of this combination was 2.3 per cent of that of malaria (4,549 cases).
   2. The incidence was 11 per cent of that of primary pneumonia.
   3. The incidence of malaria associated with pneumonitis (82 cases) in the military personnel, which was a better studied group, as compared with that of malaria (2,237 cases) was 3.7 per cent.

B.

Season		No. of Cases
Year	Month	
1942	January	1
	February	2
	March	1
	April	8
	May	12
	June	15
	July	12
	August	7
	September	14
	October	10
	November	9
	December	12
1943	January	12
	February	2
	March	2
	April	3
	May	3
	Total	125

9. Epure, V.: Pulmonary Manifestations of Malaria, Rev. san. mil., Bucuresti **37**:276-279 (April) 1938.
10. Guseyn-Zade, A.: Course of Croupous Pneumonia in Malaria Patients, Klin. med. **16**:237-238, 1938.
11. López, J. A.: Chronic Malaria as the Cause of Frequency of Pneumonia in Malaria Districts of North East Region of Argentina, Semana méd. **1**:1136-1141 (May 1) 1930.
12. Spencer, H. A.: Pulmonary Conditions Associated with Malaria Bronchomycoses, J. Trop. Med. **34**:106-108 (April 15) 1931.
13. Fauci, R.: Pneumonia from Malaria with Violent Hiccup Due to Phrenic Neuralgia: Case, Morgagni **73**:109-116 (Jan. 18) 1931.
14. Abbasov, I. G.: Malarial Pneumonia: Rare Case, Vrach. delo **15**:529-530, 1932.
15. Calò, R.: Malarial Pneumonia: Case, Rinasc. med. **9**:396 (Sept. 1) 1932.
16. Mailyan, L. M.: Pulmonary Edema of Malarial Origin, Sovet. med. (no. 4) **5**:12-13, 1941.
17. Padoan, M., and Corseri, R.: Pleurisy During Chronic Malaria: Clinical and Roentgen Study of Cases, Gior. veneto di sc. med. **10**:308-317 (May) 1936.
18. Campbell, E. T.: Primary Atypical Pneumonia and Malaria, War Med. **3**:249-255 (March) 1943.

Analysis of Symptoms.—Acute and gradual onset occurred with equal frequency; and symptoms in the upper respiratory tract preceded constitutional manifestations in 20 per cent of the cases. The chief complaints in order of frequency were: fever, cough, chills, headache, expectoration, malaise, general aches, gastrointestinal symptoms, pain in the chest, disturbances in the upper respiratory tract and excessive sweats. The following tabulation records the details of the symptoms in this group:

	No. of Cases	Percentage
A. Onset		
1. Acute (within 48 hours)	59	48.0
2. Gradual (more than 48 hours)	64	52.0
3. Not recorded	2	....
B. Respiratory symptoms preceding systemic	25	20.0
C. Symptoms (order of frequency)		
1. Systemic		
(*a*) Fever	113	90.4
(*b*) Chills	82	65.6
(*c*) Headache	58	46.4
(*d*) Malaise and weakness	41	32.8
(*e*) General aches	40	32.0
(*f*) Gastrointestinal disturbances	33	26.4
(*g*) Excess sweats	13	10.4
(*h*) Other		
(1) Cerebral psychosis	2	1.6
(2) Dysuria	2	1.6
(3) Nuchal rigidity	1	0.8
2. Respiratory		
(*a*) Cough	111	88.8
(*b*) Expectoration	46	36.8
(*c*) Pain in the chest	25	20.0
(*d*) Disturbances in upper respiratory tract	24	19.2
(*e*) Dyspnea	5	4.0
(*f*) Hemoptysis	1	0.8
(*g*) None	10	8.0

Analysis of Physical Signs.—The chief findings were rales, bronchovesicular breath sounds and dulness. There was absence of objective signs in a considerable proportion of cases, 36 per cent, attesting to the importance of roentgen examination. Positive findings referable to malaria were not prominent. The following tabulation records the objective signs:

	No. of Cases	Percentage
A. Referable to the chest		
1. Rales	66	52.8
2. Bronchovesicular to bronchial breath sounds	21	16.8
3. Dulness	17	13.6
4. Manifestations in upper respiratory tract	13	10.4
5. Diminished breath sounds	9	7.2
6. Friction rub	3	2.4
7. Dyspnea	2	1.6
8. Wheezes	1	0.8
9. None	45	36.0
B. Referable to malaria		
1. Enlarged spleen	14	11.2
2. Splenic tenderness	8	6.4
3. Enlarged liver	3	2.4
4. Hepatic tenderness	1	0.8

Roentgen Findings.—In 121 of 125 cases, or 97.8 per cent, roentgen examination was utilized for diagnostic purposes. The lesions were mainly of lower lobe distribution and of the lobular type. There were no serious complications. The following tabulation presents the results of the roentgen studies:

	No. of Cases	Percentage
A. Type of lesion		
1. Lobular	113	93.4
2. Lobar	6	5.0
3. None	2	1.6
B. Distribution		
1. Single lobes		
(*a*) Lower lobe of right lung	50	42.9
(*b*) Lower lobe of left lung	35	29.0
(*c*) Upper lobe of right lung	10	8.3
(*d*) Middle lobe of right lung	8	6.6
(*e*) Upper lobe of left lung	4	3.3
2. Multiple lobes		
(*a*) Bilateral	10	8.3
(*b*) Right side	2	1.6
(*c*) Left side	0	0.0
C. Complications		
1. Prolonged resolution	8	6.6
2. Spread (migratory)	7	5.8
3. Pleural effusion	3	2.5
4. Spontaneous pneumothorax	1	0.8
D. Physical signs preceding positive roentgen evidence	3	2.5

Laboratory Data.—The numbers of cases of estivoautumnal and of tertian malaria associated with pneumonitis were about equal (table 1). There was no significant difference between the two groups in the clinical course or in the response to therapy. Specimens of sputum studied by culture, in approximately half of the cases, revealed a preponderance of negative results (table 2). Bacteria were identified in about

TABLE 1.—*Recurrence, Severity* and Therapeutic Response of Malaria†*

				Number of Cases					
				Severity			Response to Therapy		
Parasite	No. of Cases	Percentage	Recurrence	+	++	+++	Good	Fair	Slow
Tertian	63	50.4	17	2	56	5	35	20	8
Estivo-autumnal	62	49.6	10	4	52	6	25	27	10

* Severity is recorded as + (mild), ++ (moderate) or +++ (severe).

† Response to antimalarial therapy is recorded as good (within two days), fair (within four days) or slow (more than four days); and is based on clinical response and conversion from a positive to a negative blood smear.

11 per cent of the specimens. The majority of the patients showed an inadequate response to sulfonamide compounds when they were employed, in marked contrast to the patients with primary pneumonitis unassociated with malaria. The great majority of patients (87.2 per cent) exhibited normal counts or leukopenic trends (table 3), once more at variance with the find-

ings in persons with uncomplicated pneumonia. Other laboratory data were of no significance. Blood cultures were made for the more seriously ill patients, and all were reported as negative.

Response of Pneumonitis to Treatment.—Chemotherapy was employed before, in conjunction with and sometimes after antimalarial treatment. Therefore, it is difficult to submit precise evaluations. In 50 cases, or 40 per cent of the total, antimalarial drugs alone were employed, and in 38 cases, or 76 per cent of this group, an adequate response of pneumonitis was observed. In 75 cases, or 60 per cent, both antimalarial drugs and chemotherapy with sulfonamide compounds were administered. A satisfactory response of the pneumonia was noted in 56 per cent. The following tabulation presents the figures for the entire series:

TABLE 2.—*Relationship of Results of Cultures of Sputum to Leukocytosis and Response to Chemotherapy*

Organism	No. of Cases	Percentage	Leukocytosis	Response to Chemotherapy: Number Treated	Response to Chemotherapy: Good Response
Negative	55	88.7	8	31	7
Pneumococcus Type IX	2				
Pneumococcus Type XXXI	1	8.1	2	4	1
Pneumococcus Untyped	2				
Streptococcus haemolyticus	1	1.6	0	1	0
Staphylococcus aureus	1	1.6	0	1	0

A. Antimalarial drugs and no sulfonamide compound (50 cases [40%])

1. Quinacrine hydrochloride

No. of cases	28
Percentage	56
Response* Good	10
Response* Fair	11
Response* Inadequate	7

2. Quinine

No. of cases	22
Percentage	44
Response Good	11
Response Fair	6
Response Inadequate	5

B. Chemotherapy (75 cases [60%]. Sulfadiazine was administered in 45 cases and sulfathiazole in 30 cases

Response:	No. of Cases	Percentage
Good	18	24
Fair	24	32
Inadequate	33	44

C. Special treatment	No. of Cases	Percentage
1. Oxygen	3	2.4
2. Intravenously administered fluids	4	3.2
3. Blood transfusion	1	0.8

* Response was recorded as good (within 48 hours), fair (within 72 hours) or inadequate (more than 72 hours).

Complications, Stay in the Hospital, Severity and Deaths.—There were no serious complications of pneumonitis, and complications of real severity occurred in only 3 cases (2.4 per cent). The average stay in the hospital was seventeen and five-tenths days. The only death that occurred in the series was due to cerebral malaria and not to associated pneumonitis. The following data furnish the details of these phases of the disease:

TABLE 3.—*White Cell Count and Differential Count*

	No. of Cases	Percentage
1. Leukopenia (below 5,000)	21	16.8
a. 75% polymorphonuclear cells or below	21	
b. Above 75% polymorphonuclear cells	0	
2. Normal (5,000 to 10,000)	88	70.4
a. 75% polymorphonuclear cells or below	81	
b. Above 75% polymorphonuclear cells	7	
3. Leukocytosis (over 10,000)	16	12.8
a. 70% polymorphonuclear cells or below	5	
b. Above 75% polymorphonuclear cells	11	

A. Complications	No. of Cases	Percentage
1. Prolonged resolution	8	6.4
2. Spread of lesion (migratory)	7	5.6
3. Fibrous pleuritis	3	2.4
4. Pleurisy with effusion	3	2.4
5. Spontaneous pneumothorax	1	0.8

B. Stay in hospital No. of Days	No. of Cases	Percentage
6-10	24	19.2
11-20	63	50.4
21-30	21	16.8
Over 30	17	13.6

Shortest period of hospitalization, 5 days
Longest period of hospitalization, 70 days
Average period of hospitalization, 17.5 days

C. Severity of pneumonitis, based on clinical course, stay in hospital and complications

	No. of Cases	Percentage
1. Mild	58	46.4
2. Moderate	64	51.2
3. Severe	3	2.4

D. Deaths: None due to pneumonitis; 1 death in series, due to malaria.

REPORT OF CASES

Several reports of illustrative cases are briefly presented:

CASE 1.—An American physician aged 28, an employee on the Panama Canal, was admitted to the hospital on Jan. 9, 1943, with chief complaints of fever, headache, backache and malaise of four days' duration. Roentgen examination on January 9 (fig. 1) showed pneumonic involvement of the upper lobe of the left lung. Treatment with sulfadiazine was instituted, but there was no response to the drug. The temperature was elevated, the symptoms persisted and the physical signs increased. The roentgenogram of Jan. 10, 1943 revealed spread of pneumonia to the middle lobe of the right lung. Several cultures of the sputum gave negative results. On January 13 estivoautumnal malaria was reported. The patient was placed on quinine therapy, and administration of sulfadiazine was discontinued. On January 15 the temperature was normal and the patient showed great improvement. Roentgen studies on January 20 showed complete resolution of the pneumonic process. This is an example of pneumonitis in malaria in which response to sulfadiazine was inadequate and response to quinine was excellent.

CASE 2.—An American soldier aged 23 was admitted to Gorgas Hospital on Jan. 20, 1943, complaining of chills, fever, supraorbital headache, backache and slight cough. Fine respiratory rales were heard over the base of the right lung. A roentgenogram (fig. 2) taken on January 20 revealed pneumonitis of the right lower pulmonary field. Estivoautumnal malaria was reported on January 20. Cultures of the sputum gave negative results. Quinacrine hydrochloride was administered, and an excellent response was noted. Sulfonamide compounds were not used. The blood smears ceased to show Plasmodium falciparum and roentgen findings of physical signs of pneumonia in the lower lobe of the right lung. This was confirmed by roentgen examination on November 9 (fig. 3). The patient was given sulfadiazine therapy in addition to quinine. He showed an excellent response to sulfadiazine and was completely well on November 14. No studies of the sputum were performed. This is an example of a probable bacterial pneumonitis superimposed on malaria with an excellent response to chemotherapy.

CASE 4.—A foreign white Salvadoran carpenter aged 24 was admitted to Gorgas Hospital on Feb. 13, 1942, with chief complaints of general malaise, lassitude,

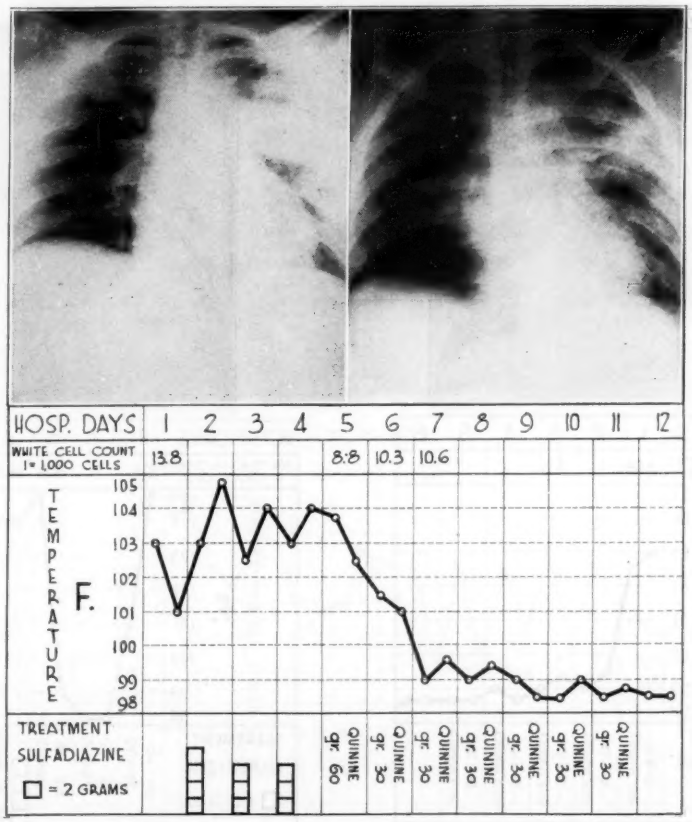

Fig. 1.—A composite chart of case 1 and the roentgen findings of Jan. 9, 1943, showing a lesion in the upper lobe of the left lung and of January 10, revealing spread to the right midzone.

pneumonitis disappeared within several days. This is an example of pneumonitis in malaria responding in a satisfactory manner to quinacrine.

CASE 3.—A British West Indian Negro carpenter aged 50 was admitted to Gorgas Hospital on Nov. 5, 1942, complaining of fever, general malaise and severe shaking chills. There were no physical signs referable to the lungs. P. vivax was found in blood films on the patient's admission. Because of the severity of the illness, he was given quinine intravenously. The temperature rapidly fell to normal, and the patient appeared improved. The blood smears failed to reveal the parasite on November 7. However, on the same day the patient's temperature rose to 105 F. and he showed muscular aches, anorexia and some tenderness over the left flank. Results of physical examination on admission were normal except for splenic tenderness. On February 14 estivoautumnal malaria was reported. He was placed on quinine therapy, but his febrile course continued. A roentgenogram taken on February 21 (fig. 4) revealed a pleural effusion with pneumonitis on the left side. The patient was then given sulfathiazole, and the response was inadequate. Cultures of the sputum gave negative results on two occasions. The symptoms and fever cleared by lysis. Roentgen studies on March 9 revealed a residual pleuritis on the left side. This is an example of atypical pneumonitis complicated by a mild pleuritis associated with malaria in which no

adequate response to sulfonamide drugs or to antimalarial drugs was noted.

CASE 5.—An American soldier aged 22 was admitted to Gorgas Hospital on May 10, 1942. At the time of his admission he was in a semicomatose state, irrational and incontinent. Estivoautumnal malaria was reported on the day of admission. On the same day signs and symptoms of pulmonary congestion developed in addition to the symptoms of cerebral malaria. No specimen of sputum was available for study. A roentgen film (fig. 5) taken on May 13 revealed a bilateral basal pneumonitis. The patient was treated with quinine intravenously, intramuscular injections of quinacrine hydrochloride, inhalation of oxygen, and sedation, and on May 15 sulfadiazine therapy was employed. Despite all therapeutic measures, the patient's condition became worse, and on May 17 he died. A postmortem examination revealed cerebral congestion and bronchopneumonia of the bases of the lungs. It is believed that this patient died because of his malarial infection and that bronchopneumonia played a minor role.

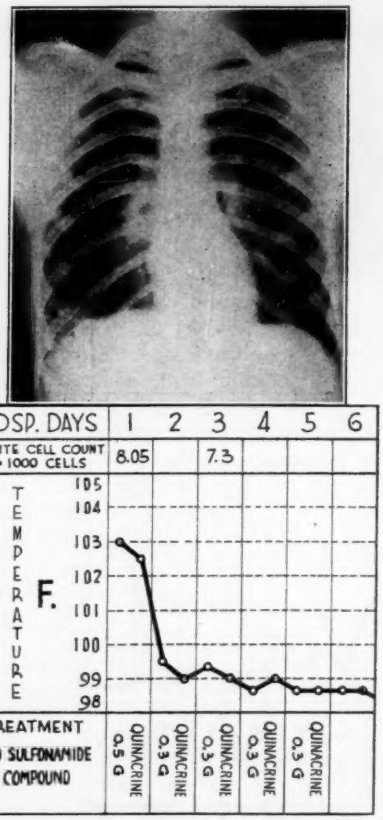
HOSP. DAYS 1 2 3 4 5 6
WHITE CELL COUNT 1-1000 CELLS 8.05 7.3
TEMPERATURE F. 105 104 103 102 101 100 99 98
TREATMENT NO SULFONAMIDE COMPOUND
QUINACRINE 0.5 G
QUINACRINE 0.3 G
QUINACRINE 0.3 G
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Fig. 2.—A composite chart of case 2 and the roentgen finding of pneumonitis of the lower lobe of the right lung on Jan. 20, 1943.

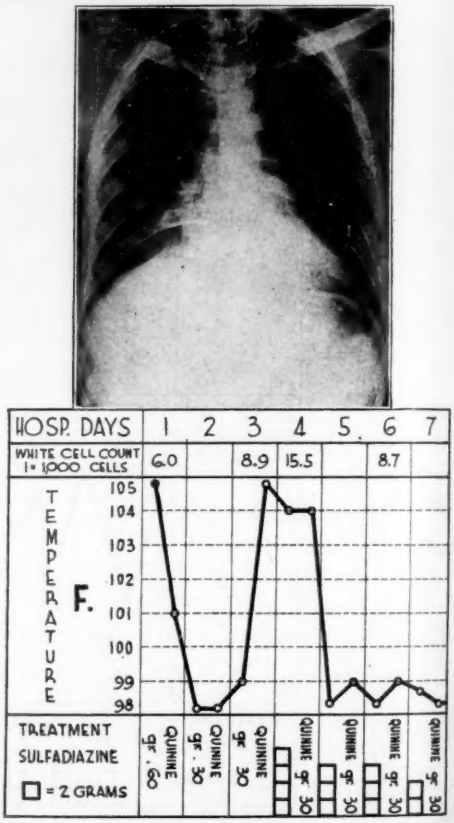
HOSP. DAYS 1 2 3 4 5 6 7
WHITE CELL COUNT 1-1000 CELLS 6.0 8.9 15.5 8.7
TEMPERATURE F. 105 104 103 102 101 100 99 98
TREATMENT SULFADIAZINE
□ = 2 GRAMS
QUININE gr. 60
QUININE gr. 30
QUININE gr. 30
QUININE gr. 30
QUININE gr. 30
QUININE gr. 30
QUININE gr. 30

Fig. 3.—A composite chart of case 3 and the roentgen findings of Nov. 9, 1942, demonstrating a lesion in the lower lobe of the right lung.

COMMENT

The incidence of pneumonitis in patients with malaria, 3.7 per cent in a selected group, is greater than the incidence of pneumonitis in the general population. The frequent association of a pulmonary lesion with this parasitic infection suggests several interesting possibilities. As in any other disease, the factor of lowered resistance plays its role. Because of the common occurrence of infections of the upper respiratory tract, as noted in malaria, foci are present for extension to the parenchyma of the lungs. There is also the problem of locus minoris resistentiae produced by the deleterious effects of the myriads of plasmodia and their toxins [19] in the pulmonary circulation. It is believed that these toxins are not only hemoclastic but also harmful to endothelial cells, with a possible destructive effect on the cellular elements of the lungs.

The recognition of a true malarial pneumonitis is another consideration. Malarial parasites and pigment in the capillaries of the lungs have been demonstrated. In the experimental

19. Strong,[4] p. 19.

work of Manwell and Goldstein [20] on the asexual cycle of Plasmodium circumflexum in birds parasites were most frequently found in the lungs, and were present in greater numbers than elsewhere. Plasmodia have been identified in the pulmonary capillaries of patients on whom postmortem examinations were performed at Gorgas Hospital.

A comparison of pneumonitis in malaria with primary pneumonitis,[21] as studied in a series of

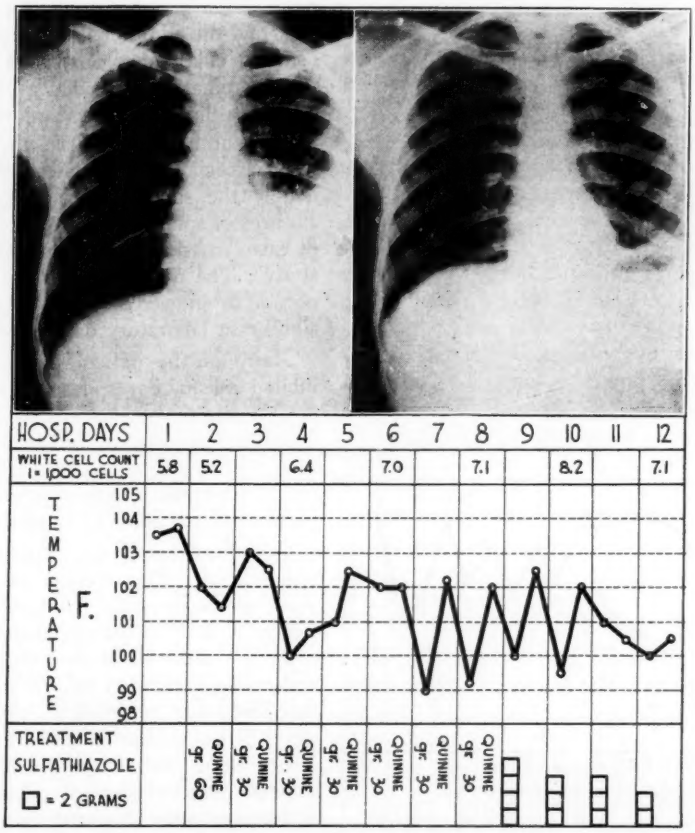

Fig. 4.—A composite chart of case 4 and the roentgen finding of a lesion in the lower lobe of the left lung and pleural effusion on Feb. 21, 1942. On March 9, 1942 marked clearing and residual pleuritis were noted.

1,000 cases which may be used as a control, indicates the similarity in the clinical picture. The seasonal occurrence of both groups reached a maximum level during the rainy season. The symptom complex, respiratory and systemic, was characterized by a mutual set of subjective findings. Absence of physical signs was more prominent in the malarial group (36 per cent) than in the group with primary pneumonitis (23.4 per cent). Roentgen studies of both groups revealed that the majority of lesions were in the lower lobes and lobular. The etiologic background based on studies of the sputum presented somewhat different problems. Although the group whose sputum failed to reveal parasites on culture was large in each series (88.7 per cent for the malarial group and 77.8 per cent for the patients with primary pneumonitis) and a virus agent was suspected in many cases, the malarial parasite was the additional factor in this study. There was a definite discrepancy in the white cell count and the differential count. Eighty-seven and two-tenths per cent of the malarial group had normal counts or leukopenia, while 53.2 per cent of the patients with primary pneumonitis presented leukocytosis. The course was rather benign in both series, and response to therapy varied chiefly in that portion of the

20. Manwell, R. D., and Goldstein, F.: Exoerythrocytic Stages in the Asexual Cycle of Plasmodium Circumflexum, Am. J. Trop. Med. **19**:279-295 (May) 1939.

21. Applebaum, I. L., and Shrager, J.: The Pneumonias in Panama: Study of One Thousand Consecutive Cases, to be published.

malarial group who responded dramatically to antimalarial drugs.

A classification of pneumonitis in malaria may be offered on the basis of the therapeutic response:

1. Atypical pneumonitis (possible virus origin), with inadequate response to therapy.
2. Bacterial pneumonitis, with satisfactory response to sulfonamide compounds.
3. Malarial pneumonitis, with excellent response to antimalarial therapy.

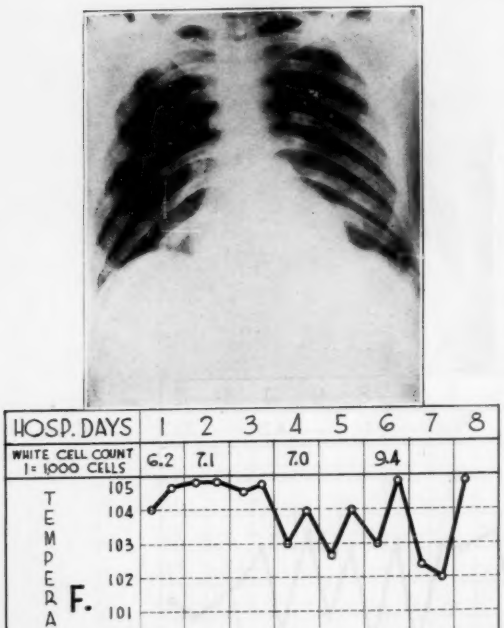
HOSP. DAYS 1 2 3 4 5 6 7 8
WHITE CELL COUNT 1 = 1000 CELLS 6.2 7.1 7.0 9.4
TEMPERATURE F. 105 104 103 102 101 100 99 98
TREATMENT SULFADIAZINE □ = 2 GRAMS
QUINACRINE I.M.
QUININE INTRAVENOUS QUINACRINE I.M.
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Fig. 5.—A composite chart of case 5 and the roentgen findings of May 13, 1942, revealing bilateral basal pneumonitis.

SUMMARY

One hundred and twenty-five consecutive patients with pneumonitis associated with malaria admitted to Gorgas Hospital in a period from January 1942 through May 1943 (seventeen months) were studied. The most important group, comprising 70 per cent of the total, consisted of young white men belonging to the military personnel. In this group the incidence of pneumonitis associated with malaria as compared with that of uncomplicated malaria was 3.7 per cent.

The disease occurred mainly during the "rainy" season and corresponded in general to the peak of the incidence of malaria and also of pneumonitis.

The symptoms, both systemic and respiratory, were similar to the subjective findings of primary pneumonitis, and the main objective signs of pneumonitis, rales, dulness and diminished breath sounds, were likewise elicited. However, there was a greater percentage of negative findings, and the additional manifestations of malaria (such as enlarged spleen) were observed. Roentgen examinations revealed a high percentage of lesions in the lower lobes and of the lobular type.

Estivoautumnal malaria and tertian malaria were associated with pneumonitis to approximately the same extent. Negative results of cultures of sputum were reported in the majority of cases in which specimens were submitted for study. The majority of white cell counts were normal or showed a leukopenic trend. No other significant laboratory data were noted.

Many of the patients with pneumonitis exhibited adequate response to antimalarial therapy; a fair proportion reacted favorably to sulfonamide compounds, and in a number the disease ran its course unaffected by therapy. Special or energetic measures were rarely employed, because of the relative benignity of the disease.

Complications of pneumonitis were few and not serious. The average stay in the hospital was seventeen and five-tenths days, slightly longer than with uncomplicated pneumonitis or malaria. Most of the patients had mild or moderate symptoms, and only 3 (2.4 per cent) had manifestations recorded as severe. There was only 1 death, due to cerebral malaria, in the entire series, and the pneumonitis was considered noncontributory. No essential racial differences were observed, but the sample is too small for accurate deductions.

In conclusion, it may be stated that pneumonitis in malaria is a relatively benign disease and may be classified on the basis of this study as follows: (1) atypical or virus pneumonitis, with inadequate response to the therapy employed, running a self-limited course; (2) bacterial pneumonitis, with adequate response to sulfonamide compounds; (3) malarial pneumonitis, with favorable response to antimalarial drugs.

Miss Estelle Hall, medical secretary of Gorgas Hospital, assisted in the compilation of data and in the preparation of the manuscript.

The Board of Health Laboratory of the Panama Canal Zone cooperated in the study.

CLINICAL SIGNIFICANCE OF THE DEEPER ANATOMIC CHANGES IN LYMPHOID DISEASES

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The term lymphoid diseases is used in this paper to designate an isolated group of interrelated diseases composed of lymphogenous leukemia, Hodgkin's disease, giant follicular lymphadenopathy, lymphosarcoma and the gastrointestinal so-called pseudoleukemia of Briquet. The object of this paper is to point out the frequency with which these diseases originate in the deeper lymphoid structures, notably in the lymph nodes of the abdomen, and the secondary significance of enlargement of the superficial nodes, when it occurs at all. If the lymphoid diseases as a group have been previously considered from this standpoint I am not aware of it. In any event, it appears to be a matter of concern both to the clinician and to the pathologist whether enlargements of superficial lymph nodes are preponderant or "primary" factors in lymphoid diseases or externalizations of preponderant or "primary" changes in the lymph nodes of the abdomen or thorax or both, in the spleen, in the thymus or in the gastrointestinal tract.

It is possible to arrive at a reasonably safe conclusion concerning the age of the aggregate of enlarged lymph nodes as compared with the age of the estimated sum total of hyperplastic lymph follicles in the spleen by guesswork based on relative sizes, and in this way to speculate on antecedence of origin. If, for example, the spleen is enormously enlarged and the aggregate of enlarged lymph nodes appears to be relatively small, it is justifiable, I believe, to assume that the changes in the spleen preceded those in the lymph nodes. If the aggregate of enlarged lymph nodes appears to be greatly in excess of the estimated sum total of the hyperplastic lymph follicles in the spleen, it is equally justifiable to assume that the hyperplastic changes in the lymph nodes preceded those in the spleen. If the aggregate of enlarged lymph nodes appears to be much the same as the sum total of the hyperplastic lymph follicles in the spleen, it may be assumed with like propriety that the lymphoid hyperplasias in the two localities commenced at the same or approximately the same time.

From the Laboratories of Pathology, Bellevue Hospital.

LYMPHOGENOUS LEUKEMIA

Lymph Nodes and Spleen.—In the laboratories of pathology at Bellevue Hospital 36 cases of chronic lymphogenous leukemia were encountered among 22,537 necropsies. Studies based on these cases confirm with almost monotonous regularity the descriptions of the anatomic changes of the disease as portrayed in current texts. In addition, certain features were brought out which no doubt have been mentioned before as individual examples but, as far as I know, have not been emphasized as a whole. I refer to the comparisons in size between the aggregate of lymph node enlargements and the size of the spleen as indicating whether the disease in individual cases arose or attained preponderance in the lymph nodes or in the spleen.

Current textbooks on medicine and pathology are apt to lead one to believe that enlargement of the superficial lymph nodes is a frequent, if not a constant, and the preponderant, anatomic feature in chronic lymphogenous leukemia. According to the records of the Bellevue Hospital necropsies this is not altogether true. Of 36 cases the superficial nodes were not enlarged in 4 (11 per cent) and were enlarged only slightly in 9 (25 per cent), moderately in 18 (50 per cent) and massively in 5 (14 per cent). The thoracic nodes were not enlarged at all in 18 cases (50 per cent) and were slightly enlarged in 3 (8.3 per cent) and massively enlarged in 15 (41.7 per cent). The retroperitoneal nodes alone were involved in 12 cases (33 per cent), 8 times massively (22 per cent) and 4 times moderately (11 per cent). The retroperitoneal and mesenteric nodes together were massively enlarged in 13 cases (36 per cent). The mesenteric nodes alone were involved in 5 cases, 3 times massively and twice moderately. The abdominal and thoracic nodes together were en-

larged in 17 of 36 cases, massively in 16 (44 per cent). In 6 cases (16 per cent) the abdominal nodes were not enlarged at all.

The weight of the spleen was recorded in 32 of the 36 cases. The lowest weight was 250 Gm. and was found in a 65 year old woman with massive enlargements of the thoracic and abdominal nodes and innumerable focal lymphomas in a liver weighing 1,880 Gm., together with generalized superficial lymphadenopathy. Microscopically the splenic follicles and the pulp were overgrown by lymphocytes. The largest spleen weighed 2,500 Gm. and extended downward to the brim of the pelvis and inward to the midline. It was found in a white man aged 32 and was accompanied by "about 100" retroperitoneal lymph nodes measuring from 0.5 to 2.5 cm. in their longest diameters. There were no enlarged superficial or thoracic nodes.

The average weight of the spleen in 32 cases was 887.96 Gm. In 1 of the 4 remaining cases the spleen was described as "slightly enlarged." In the other 3 it measured 18, 21 and 22 cm. in length. The spleen was preponderantly or "primarily" enlarged in 10 cases. The weights were 1,500, 1,450, 950, 700, 460, 1,170, 2,085, 800, 480 and 2,500 Gm. In 3 of these cases the superficial lymph nodes were not enlarged. In the 10 cases, with the 3 exceptions noted, there were various combinations of enlarged superficial thoracic and abdominal nodes. However, the aggregate of these did not approach the estimated sum total of lymphoid hyperplasias in the spleen.

According to necropsy experience at Bellevue Hospital, enlargement of the superficial nodes in lymphogenous leukemia is not necessarily present and when present it may be of slight or moderate degree in a large percentage of cases; massive enlargement is not by any means a common occurrence; there is absence of enlargement of thoracic lymph nodes in a large percentage of cases; combined enlargement of thoracic and abdominal nodes occurs in a high percentage, and the spleen may attain massive proportions unaccompanied by anything approaching a corresponding degree of enlargement of the lymph nodes in the aggregate.

In one group of cases, lymphogenous leukemia shows itself in the form of preponderant or, if one chooses, "primary" enlargement of the abdominal lymph nodes followed by enlargement of the spleen, and in a second group it produces preponderant or "primary" enlargement of the spleen followed by enlargement of the lymph nodes of the abdomen alone or of the abdomen and chest together. According to the Bellevue Hospital necropsy experience, lymphogenous leukemia is preponderantly or "primarily" a disease of the abdominal lymphoid organs. On the basis of the same experience lymphogenous leukemia does not produce preponderant changes in the lymph nodes of the thorax or of the superficial nodes. Enlargement of either of these groups of lymph nodes, when it occurs, is a late manifestation of preponderant involvement of other lymphoid structures alone or in various combinations, such as preponderant enlargement of the abdominal nodes alone, of the abdominal and thoracic nodes in combination with one another, or of the spleen in combination with enlargement of the abdominal nodes or with enlargement of both the abdominal and the thoracic nodes. If these statements are universally and not merely locally true, they indicate that the causative agent of chronic lymphogenous leukemia enters not through the respiratory tract but through the mouth. Further substantiation of this statement is suggested by the fact that in both acute and chronic lymphogenous leukemia the lymph follicles of the intestinal tract, especially in the ileum, may be hyperplastic, sometimes to a remarkable extent, indicating reaction to an inimical agent. At Bellevue Hospital, in addition to 36 cases of chronic lymphogenous leukemia investigated at necropsy, there were 4 cases of acute leukemia. In the 40 cases the intestinal tract was involved 14 times (35 per cent), 11 times in chronic and 3 times in acute lymphogenous leukemia. In the 14 cases of intestinal involvement the solitary and agminated follicles were hyperplastic alone or in combination. In the majority of instances these hyperplasias were negligible anatomically and consisted of slight or moderate enlargements of the lymph follicles, most marked in the ileum but not confined to that region. In some cases Peyer's patches were hyperplastic, occasionally attaining a length of 5 cm. In a few instances they were superficially ulcerated. In 2 cases the intestine was affected to a remarkable extent. In these cases the changes, although unusual as far as lymphogenous leukemia is concerned, were replicas in miniature of those in the intestine in the gastrointestinal so-called "pseudoleukemia," or, if one prefers it, in lymphosarcomatosis of the gastrointestinal tract. One case was that of a Negro aged 31. The cervical, axillary and inguinal nodes were slightly enlarged. There were "one or two enlarged peribronchial nodes"; otherwise the thorax was free from enlargement of lymph nodes. The mesenteric and retroperitoneal nodes were extremely numerous, were discrete and varied in diameter from 0.5 to 2.5

cm. The spleen was enlarged, measuring 21 by 7 by 6 cm. Its weight was not recorded. Throughout the intestinal tract the mucous membrane was elevated by countless numbers of hyperplastic follicles. They were most numerous in the ileum, especially in its lower two thirds, but present also in the large intestine. All of Peyer's patches were hyperplastic. In a second case, that of a boy 13 years of age, dead of acute lymphogenous leukemia, the ileum showed numerous transverse ulcers varying from 1 to 2 cm. in length. The edges were elevated to the extent of about 2 mm. The craters were grayish, in places necrotic and in other places freshly hemorrhagic. Some of the ulcers in the upper part of the ileum were superficial. Most of those in the lower third were deep and extended through the musculature to the serosa, which was edematous, injected and covered by fibrinous exudate. There were no perforations. Microscopically, the ulcers were rimmed by closely packed lymphocytes, sometimes mixed with red cells or with small deposits of fibrinoid material. Polymorphonuclear leukocytes were not observed. Peyer's patches were unaffected except for a mild degree of hyperplasia and an occasional area of superficial ulceration. In 1 case there was widespread hyperplasia of lymphoid collections at the pyloric end of the stomach. In another case the lymph follicles in the esophagus projected beneath the mucosa in considerable numbers. In only a few of the necropsies was it permitted to remove the structures of the mouth and throat. However, in 2 cases the lingual tonsils were markedly hypertrophied, and the faucial tonsils were hypertrophied in 1 case.

Liver.—The livers were weighed in 21 of the 36 cases of chronic leukemia (16 men and 5 women). The smallest weight was 1,230 Gm. and the largest 3,900 Gm. The average weight was 2,389.52 Gm., or about 800 Gm. above the average for men, which is usually placed at 1,500 Gm., or a few grams above the average for women. The livers in 3 other cases were described as "normal size," "enlarged" and "markedly enlarged" respectively.

Kidneys.—The kidneys were involved in 10 (27 per cent) of the 36 cases. In 7 cases the organs were not noticeably enlarged, but in all they were diffusely infiltrated by lymphocytes. In 1 of the 3 remaining cases both kidneys were enlarged and measured 14.7 by 5.4 cm. and both were richly infiltrated by lymphocytes. In a second case the kidneys together weighed 450 Gm., and in a third case, 900 Gm. In both cases the kidneys were extensively infiltrated. In all of the 3 cases the lymphocytes lay in the connective tissues. In some instances they were loosely sprinkled. In other cases the kidneys from capsule to pelvis were buried in dense lymphocytic collections. With the exception of 2 cases in which the urine showed an excess of albumin, no instance was recorded of functional disturbances due to the changes described.

Thymus.—Investigators are agreed that Hassall's corpuscles and the reticulum cells of the thymus from which they spring are epithelial. The derivation of the chief elements of the organ, namely, the small cells, has been the subject of debate. Maximow believed that early in its development the thymus is invaded by mesenchymal elements which differentiate into lymphocytes and that these accumulate in such numbers as to give the organ the appearance of a lymphoid structure. Maximow's belief in the lymphocytic nature of the small cells has been opposed by Stöhr and others but concurred in by Hammer, Schaffer and Pappenheimer. The conception of the small thymic cells as lymphocytes is in keeping with the knowledge of the pathology of the thymus, especially of certain growths which spring from it or from its remains, notably the lymphosarcomas and Hodgkin's disease. In addition, the histologic picture of the fully developed thymus shows not only that its origin is to be traced to two separate sources but that it is related to the lymph nodes. The cortex is composed of densely packed cells which are structurally identical with small lymphocytes. In the medulla the same small cells are present, but they are loosely packed and in lesser numbers. In the midst of them and standing out in contrast are the large epithelial whorls, or Hassall's corpuscles, together with a delicate epithelial reticulum. In the human thymus, also, lymph follicles have been demonstrated (Wegelin), but their presence is inconstant. They appear with greater frequency in certain lower animals, especially in cats.

It remains to trace the relationship, if any, of the thymic lymphocytes to lymphogenous leukemia. Little is known of this aspect of the pathology of the thymus. The subject is open for discussion whether the enlarged thymus which is sometimes found in chronic lymphogenous leukemia produces lymphocytes in excessive numbers and contributes to the process of leukemia or whether the thymus in lymphogenous leukemia enlarges secondarily in response to infiltration of lymphocytes from the blood. One of the cases in the Bellevue Hospital series tends to throw light on this phase of the subject. It was that of a Negro 35 years of age. The

thymus lay free in the midline of the superior mediastinum. It measured 8 cm. in length and weighed 48 Gm. The organ was bilobed, and the apex pointed downward. It was pinkish and of fleshy consistency. In the vicinity were great numbers of discrete lymph nodes measuring 0.5 to 3 cm. in their longest diameters. Microscopically the markings of the thymus were obscured by hordes of lymphocytes, among which were the remains of a few Hassall corpuscles. The spleen weighed 630 Gm. and was rich in lymphoid cells. The retroperitoneal nodes were enlarged to form huge masses, the individual nodes in them measuring from 0.5 to 5 cm. in diameter. The changes in the thymus were of scant proportions as compared with those in the abdominal and thoracic lymph nodes and spleen, which were overwhelming. The thymus was obviously persistent and secondarily infiltrated.

HODGKIN'S DISEASE

It is a sort of tradition in medicine that Hodgkin's disease is a primary or preponderant disease of the cervical lymph nodes. This conception, however honored by time and repetition, is contradicted by fact. Reed [1] maintained that the disease "almost always begins in the cervical region" and that "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere." She based this conclusion on 8 cases investigated at Johns Hopkins Hospital, in 3 of which necropsy was performed. Longcope [2] voiced a similar opinion on the basis of a study of 8 cases at the Pennsylvania Hospital, in 3 of which necropsy was performed. At Bellevue Hospital, in 30 cases investigated by necropsy preponderant enlargement of the cervical nodes was encountered once only (0.3 per cent). In 10 of the 30 cases, or in 33 per cent, the preponderant enlargement occurred in the abdominal lymph nodes; in 9 cases, or 30 per cent, the lymph nodes of the chest and abdomen were preponderantly enlarged in combination with one another. In other words, preponderant Hodgkin's disease of the abdominal lymph nodes or of the combined abdominal and thoracic nodes occurred in 63 per cent of 30 cases in which post mortem examination was done—a ratio of 19 to 1. In 7 of the 30 cases the superficial nodes were not involved (23 per cent); in 13 they were involved to a slight extent (43 per cent), and in the remaining 10 cases (33 per cent), they were moderately or markedly enlarged in association with collections in the deeper parts that were of massive proportions. From combined necropsy and clinical experience it appears that the changes in the deeper lymph nodes are "primary," that they may remain apparently dormant for months or even for years, giving rise to no symptoms or signs on which one may safely predicate the diagnosis of Hodgkin's disease, and that if enlargement of the superficial nodes occurs it is a late signal and indicates that the disease has attained widespread proportions in the abdomen or in the abdomen and thorax. It is a matter of clinical value—not necessarily of anatomic sequence—that enlargement of the axillary nodes suggests predominant involvement of the thoracic groups and that inguinal adenopathy suggests preponderant involvement of the abdominal nodes. Enlargement of the axillary or inguinal nodes independent of such associations, if it exists, was not recognized in the Bellevue Hospital series.

Spleen.—In some instances the burden of Hodgkin's disease is borne by the spleen almost alone, an opinion which I ventured to express [3] in 1909 when I described the case of a girl 17 years of age who for three years before admission to the New York Hospital knew that there was a mass in the left side of her abdomen. The superficial lymph nodes were not enlarged. The edge of the spleen was felt just above Poupart's ligament on the left side, whence it could be traced to the right as far as the umbilicus and thence upward. The organ was removed at operation and measured 25 by 18 by 8 cm. Microscopic examination revealed the histologic changes of Hodgkin's disease. At the time of operation no enlarged lymph nodes were seen or felt in the abodmen. Death occurred, but necropsy was not obtainable. Since then I have encountered 2 other cases in which the spleen was removed at operation. One was that of a woman whose spleen reached into the pelvis and as far forward as the mamillary line. After several weeks a barely palpable lymph node appeared in one of the anterior cervical triangles. The node was removed, and microscopic examination showed the histologic picture of Hodgkin's disease. From an Italian woman 38 years of age operated on by Carlucci [4] at Bellevue

1. Reed, D. M.: Johns Hopkins Hosp. Rep. **10**:133, 1902.

2. Longcope, W. T.: Bull. Ayer Clin. Lab. Pennsylvania Hosp., 1903, no. 1, p. 4.

3. Symmers, D.: Certain Unusual Lesions of the Lymphatic Apparatus, Including a Description of Primary Hodgkin's Disease of the Spleen and a Case of Gastrointestinal Pseudoleukemia, Arch. Int. Med. **4**: 218 (Sept.) 1909.

4. Carlucci, G.: Personal communication to the author.

Hospital, a spleen weighing 830 Gm. was removed. No enlargements of superficial or of abdominal lymph nodes were detected. Six weeks later the patient became jaundiced and an enlarged lymph node was found obstructing the common bile duct. Within eighteen months death occurred as a result of extensive Hodgkin's disease of the abdominal nodes and involvement of the spinal cord following pressure on and erosion of the vertebral column. Three cases of like description have been recorded by Wade,[5] Dowd[6] and Mellon,[7] in all of which the spleen was removed surgically. Evidence of this sort, while suggestive, is inconclusive. On the other hand, a series of 6 cases was encountered at Bellevue Hospital in which at necropsy the spleen was massively increased in size, weighing on an average 1,136 Gm., or 936 Gm. above the high normal weight. There were associated enlargements of lymph nodes, usually in the abdomen and occasionally in the neck, but their size and number were insignificant as compared with the extent to which the spleen was involved. Two other examples of preponderant Hodgkin's disease of the spleen, likewise verified at necropsy, have been recorded by Cornwall and by l'Esperance. Krumbhaar's[8] case of Hodgkin's disease of the bone marrow and spleen without apparent involvement of the lymph nodes appears to me to be another example of preponderant or "primary" Hodgkin's disease of the spleen, although the full extent of the changes in the marrow was not determined at necropsy, only a relatively small amount having been removed for histologic study. It would seem that evidence adduced at necropsy proves beyond reasonable doubt the existence of a variety of Hodgkin's disease in which the spleen is "primarily" involved.

Of the 30 cases in the Bellevue Hospital series the spleen was "secondarily" enlarged in 20, or in 66 per cent. The average weight was 801 Gm., or 601 Gm. in excess of the high normal weight.

Thymus.—Participation of the thymus as the preponderant or "primary" lesion in Hodgkin's diseases is well recognized. In 1904, Yamasaki[9] recorded the case of a woman 32 years of age, who at necropsy presented a huge mass in the superior mediastinum that imitated the shape of the thymus. It covered the precordium and penetrated the parietal pericardium at several points. The growth involved the pleura of the right lung and compressed the substance of the lung itself. The sternum was eroded, and the walls of the left innominate vein and of the superior vena cava were infiltrated. The lymph nodes in the neck and in the region of the stomach were slightly enlarged. At least 7 additional cases have been recorded, 1 by Chiari,[10] 1 by Lyon[11] and 5 by myself.[12] In all of the 8 cases the thymic growths were enormous. In 6 cases the cervical nodes were not enlarged, and in 2 cases they were slightly or moderately enlarged. In 3 cases there were moderate numbers of enlarged nodes in the thorax and abdomen, while in a remaining case the retroperitoneal nodes were numerous and greatly enlarged. In 5 cases there was no involvement of the spleen, and in 3 the spleen was slightly or moderately enlarged and nodular. In all of these cases the histologic picture was that of Hodgkin's disease.

Liver.—In 17 of the 30 cases observed at Bellevue Hospital (58 per cent) the liver presented foci of characteristic histologic changes, varying in diameter from 0.5 to 2 cm. Microscopic examination showed that the nodules arose in the periportal spaces and were initiated by hyperplasia of lymphoid cells lying in the walls of the portal veins. In 1 case, the patient, a woman aged 40, was admitted to Bellevue Hospital and died twelve days later. She complained of cough of two weeks' duration, but principally of enlargement of the abdomen that had been progressing for three months, attended by pains in the epigastrium and the chest. The patient was profoundly emaciated. The skin was tinged slightly yellow. The abdomen was prominent, and there were signs of a fluid wave and of shifting dulness. The lower edge of the liver was palpated at the level of the umbilicus. The spleen was not felt. After paracentesis and the removal of 4,400 cc. of clear yellow fluid the edge of the spleen was palpated in the anterior axillary line. At necropsy the abdomen contained about 500 cc. of clear fluid. The liver was enormously enlarged, the lower margin lying at the level of the umbilicus. Its shape was well preserved. The surface was smooth, except for a number of whitish nodules, the largest of which were about 5 mm. in diameter. The substance of the liver was permeated by large, smooth bands of fibrous tissue which followed the distribution of the portal

5. Wade, H. W.: J. M. Research **29**:209, 1913.
6. Dowd, C. N.: Ann. Surg. **65**:785, 1917.
7. Mellon, R. R.: Am. J. M. Sc. **151**:704, 1916.
8. Krumbhaar, E. B.: Am. J. M. Sc. **182**:764, 1931.
9. Yamasaki, M.: Ztschr. f. Heilk. **5**:269, 1904.
10. Chiari, O. M.: Centralbl. f. allg. Path. u. path. Anat. **22**:8, 1911.
11. Lyon, M. W.: Am. J. M. Sc. **158**:557, 1919.
12. Symmers, D.: Ann. Surg. **95**:544, 1932.

system. At the time of necropsy it was estimated that two thirds of the parenchyma was thus replaced. The mesenteric and retroperitoneal lymph nodes were moderately increased in number and varied in diameter from 1 to 3 cm. No other enlarged lymph nodes were encountered in any part of the body. The spleen was of normal size. Microscopic examination of the liver showed extensive replacement of the parenchyma by bands of connective tissue which occupied the portal spaces and expanded in such fashion as to produce atrophy of the hepatic lobules and the bile ducts by pressure. In practically every one of them was a small portal vessel encircled by a mantle of lymphocytes, among which were mononuclear giant cells and occasionally a giant cell of the megakaryocytic type. In the spleen microscopic examination showed great thickening of the larger veins, the walls of which were reenforced by connective tissue in which were groups of lymphoid cells and a few mononuclear giant cells, together with conspicuous numbers of cells of the megakaryocytic type. The lymph nodes were extensively replaced by fibrous tissue, which was poorly nucleated and presented a glazed, hyaline appearance. In the intervals were collections of lymphoid cells with an occasional mononuclear giant cell and a fairly liberal sprinkling of giant cells of the megakaryocytic type. The veins in the medulla of the adrenal capsule were thickened, and in their walls were collections of lymphocytes and rarely a multinuclear giant cell. As far as I have been able to learn, this case presents a unique feature in the pathologic picture of Hodgkin's disease, in that the lesion was preponderant or "primary" in the liver. In another case the patient was jaundiced and the abdomen was filled by fluid. The liver was riddled by nodules lying in the substance of the organ and projecting above the surface so that the appearance to the naked eye simulated that of cirrhosis. At the hilus and compressing the portal vein and the common bile duct was a group of enlarged lymph nodes, the largest measuring 1 by 1.5 cm. In still another case a huge mass surrounded the portal vein shortly after it entered the liver and appeared both to the naked eye and on microscopic examination to arise in the walls of the vein and thence to extend concentrically in such fashion as to push aside the adjacent hepatic tissues. In addition, innumerable microscopic foci of the same histologic structure were seen in the periportal connective tissues. In other words, it appears that in certain instances the changes in the liver in Hodgkin's disease are of clinical significance in that they are capable of producing the signs of cirrhosis. In the remaining 13 cases the changes in the liver gave rise to no clinical signs indicative of obstructive disturbance.

Gastrointestinal Tract.—In a good many instances ulcerative growths of the pyloric end of the stomach removed at operation have been recorded under the diagnosis of "primary" Hodgkin's disease. The objection presents itself not only that examination was necessarily limited to the field of operation and remote lesions in other parts could not be excluded but that convincing histologic evidence was not adduced. However, in 1 case it has been shown at necropsy and by subsequent microscopic examination that the stomach was the seat of preponderant or "primary" Hodgkin's disease. The case was recorded by Singer,[13] and the anatomic and microscopic diagnoses were made by the late R. H. Jaffé. The illustrations which accompany Singer's paper are convincing. Postmortem examination showed a large infiltrating growth proximal to the pyloric ring on both curvatures. The lymph nodes in the gastrohepatic omentum were enlarged, the largest measuring 3 cm. in diameter. None of the changes of Hodgkin's disease was found in any other part of the body. That Hodgkin's disease of the gastrointestinal tract is rare is further exemplified by the fact that in the combined experience of Bellevue, Kings County, City and Queens General hospitals not a single example was found among 173 necropsies in cases of Hodgkin's disease.

GIANT FOLLICULAR LYMPHADENOPATHY

As far as I have been able to learn, only 3 necropsies have been recorded in cases of giant follicular lymphadenopathy. Terplan[14] contributed 1 report under the heading "A Peculiar Granuloma-like Systemic Disease." The cervical nodes were described as about "the size of a bean," as were the axillary and supraclavicular nodes. The superficial and deep inguinal nodes were from "bean to hazelnut size," occasionally "the size of a prune." The retroperitoneal nodes were greatly enlarged, forming clusters the "thickness of one's finger"; others were discrete and ranged in size from that "of a cherry to that of a hazelnut." The spleen was enlarged and measured 20 by 13 by 8 cm. From Terplan's descriptions I should guess that the sum total of the enlarged abdominal lymph nodes and

13. Singer, H. A.: Primary, Isolated Lymphogranulomatosis of Stomach, Arch. Surg. **22**:1001 (June) 1931.

14. Terplan, K.: Verhandl. d. deutsch. path. Gesellsch. **24**:65, 1929.

of the lymphoid hyperplasias in the spleen greatly exceeded that of the enlarged nodes in the neck, axillas and groins.

I have recorded 2 necropsies in cases of giant follicular lymphadenopathy.[15] In 1 of them the superficial nodes were not enlarged. The retroperitoneal nodes formed an enormous mass in which the largest nodes measured from 3 to 5 cm. in diameter. The hypogastric and the anterior inguinal nodes were similarly enlarged and varied in diameter from 4 to 5 cm. The lymph nodes in the region of the hilus of the liver, the perigastric and the peripancreatic nodes and the nodes at the hilus of the spleen were enlarged. The largest among them were about 4 cm. in their longest diameters. The mesenteric nodes were numerous and enlarged to the size of 3 or 4 cm. The spleen weighed 900 Gm. In the other case the cervical lymph nodes on both sides were palpable, discrete and measured from 0.5 to 2 cm. in diameter. The axillary lymph nodes on both sides were similarly enlarged. The abdominal lymph nodes were enlarged to an enormous extent. The abdominal aorta, the iliac arteries and the inferior vena cava were embedded in masses of closely packed nodes measuring on the average about 3 cm. in their longest diameters. In other areas the nodes were enlarged but discrete. The spleen weighed 160 Gm.

In a patient whom I observed in the wards at Bellevue Hospital, operation revealed that the retroperitoneal lymph nodes were enlarged to form an immense growth in which the individual nodes measured from 1 to 6 cm. in their longest diameters, while the nodes in the neck and groin were enlarged in small numbers and varied in diameter from 1 to 1.5 cm. The spleen was palpable 6 cm. below the left costal slope. This case still further confirms the existence of a form of giant follicular lymphadenopathy in which the preponderant or "primary" disease involves the lymphoid structures of the abdomen, especially the lymph nodes, corresponding in this respect to preponderant Hodgkin's disease and to lymphogenous leukemia of the abdominal lymphoid organs.

Finally, there is a form of giant follicular lymphadenopathy in which the spleen seems to be preponderantly or "primarily" enlarged without or with only negligible involvement of the abdominal lymph nodes and with no or relatively negligible involvement of the superficial nodes.

15. Symmers, D.: Clinical Significance of Pathologic Changes in Giant Follicular Lymphadenopathy, Arch. Path. **34**:385 (Aug.) 1942.

In Becker's[16] case of giant follicular lymphadenopathy, the first to be described, the spleen was enlarged out of all proportion to the size of the clinically detectable enlarged lymph nodes. Some years later Brill, Baehr and Rosenthal[17] published 2 cases of like description. In 1 of them the spleen was huge, reaching from the level of the eighth rib on the left to the anterior superior spine of the ilium and to the right for a distance of 5 cm. beyond the midline of the body. The superficial lymph nodes were enlarged but only to a comparatively insignificant extent. In a second case the spleen reached from the eighth intercostal space on the left to the brim of the pelvis within 2 cm. of the middle line, while the superficial lymph nodes were only moderately enlarged. A case of the same sort has been recorded by Decker and Little,[18] and I have reported another.[15] In both of them the enlarged spleen was removed at operation. In Decker and Little's case no enlargement of the superficial nodes was noted but two nodes were found in the gastrosplenic omentum, the larger measuring 2 cm. in its longest diameter. In my case there were no detectably enlarged superficial nodes and no enlarged nodes were found in the abdomen. Three cases of almost identical description in which the enlarged spleens were removed at operation have been reported by de Jong.[19] Nevertheless, in the absence of evidence revealed by necropsy the existence of preponderant or "primary" giant follicular lymphadenopathy of the spleen cannot be affirmed.

LYMPHOID HYPERPLASIA OF THE APPENDIX

In about 10 per cent of all appendixes, especially in children and young adults, the mucosa contains collections of large lymph follicles each of which is provided with a germinal center whose cell contents differ in no essential from those of other lymphoid nodules. As age advances these follicles tend to diminish in size and may even disappear. However, in early life they may undergo both numerical and dimensional hyperplasia, encroaching on the lumen and compressing the submucosa and muscularis,

16. Becker, E.: Deutsche med. Wchnschr. **27**:726, 1901.

17. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen, J. A. M. A. **84**:668 (Feb. 28) 1925.

18. Decker, H. R., and Little, H. G.: Malignant Hyperplasia of Lymph Follicles of Spleen, J. A. M. A. **105**:932 (Sept. 21) 1935.

19. de Jong, R. de J.: Beitr. z. path. Anat. u. z. allg. Path. **69**:185, 1921.

producing symptoms and signs of "chronic appendicitis," including one or several episodes characterized by colicky sensations or pain and tenderness in the region of the appendix, with or without a slight degree of muscular rigidity, nausea and, occasionally, vomiting. The temperature, pulse and leukocyte count with minor exceptions remain within normal limits. Repeated attacks of this description may end in sclerosis of the appendix and partial or even complete obliteration of the lumen. This type of lymphoid hyperplasia of the appendix occurs most commonly in persons with status lymphaticus and in their cases the question of operative removal assumes more than ordinary importance.

Evidence is accumulating to show that hyperplasia of lymph follicles in the appendix may occur in notable excess of that met with in persons with appendixes of the type just mentioned. In such circumstances not only are the follicles increased in size and number, but they may expand in such fashion as to encroach on the lumen and to bring about almost complete replacement rather than simple compression of the mucosa and muscularis, sometimes being limited externally by the serous covering and a layer of compressed and atrophic muscle fibers. Dr. James R. Lisa and I have recently encountered 9 cases of involvement of this general description. The patients were about equally distributed between males and females from 6 to 38 years of age. In addition to the symptoms and signs just enumerated, 3 patients had occasional elevations of temperature to from 101 to 104 F. In all of the appendixes the lymph follicles were enormous, corresponding in practically every particular to those in the lymph nodes of giant follicular lymphadenopathy, including curious configurations, the shape, for instance, of a boat or a kidney or a hook.

In status lymphaticus lymphoid hyperplasia of the appendix is part of a more or less generalized hyperplasia of all the lymphoid depots, especially in the gastrointestinal tract and the spleen. Whether the same is true of lymphoid hyperplasia of the appendix of the type just referred to remains to be shown by necropsy. Nevertheless, its clinical significance, like that of the appendix in status lymphaticus, is obvious.

GASTROINTESTINAL SO-CALLED PSEUDOLEUKEMIA OF BRIQUET

Shortly after the discovery of lymphogenous leukemia independently by Bennet and Virchow, Cohnheim, under the title of pseudoleukemia, described a disease presenting the anatomic characteristics of lymphogenous leukemia without corresponding changes in the blood, at least according to the hematologic standards of that time. It is now widely accepted that Cohnheim's original case of pseudoleukemia was in reality an instance of that variety of lymphogenous leukemia in which the white cells are reduced in number and among which are abnormal forms—the so-called aleukemic leukemia, or, if one chooses, aleukemic myelosis. It is difficult to decide which of the three designations is the most inappropriate. In 1838 Briquet described and illustrated a remarkable lymphoid disease which has since received the equally dubious designation of gastrointestinal pseudoleukemia. It seems to be a clinical and pathologic entity. Although it lacks the infiltrating and destructive qualities of a malignant tumor, it is nevertheless regarded by some as a form of lymphosarcoma. The lesions arise in the mucosa and project above it. Thus far only 12 cases have been recorded, but the disease is probably commoner than the number of published cases indicates, 2 well marked examples and a third of comparatively limited proportions having come to my own attention. Anatomically, the disease is marked by an almost incredible degree of lymphoid hyperplasia extending from the base of the tongue through the esophagus, stomach and intestine, including the appendix, to the anus, oftenest in the form of closely packed nodules, most numerous in the stomach and intestine, varying in diameter from 1 to 5 mm., but sometimes projecting as polypoid masses measuring several centimeters in height. Peyer's patches are often hyperplastic to an extreme degree, occasionally ulcerated. The spleen is practically always greatly enlarged, as are the lymph nodes of the abdomen and chest. The superficial nodes in various localities are apt to participate to an almost equally remarkable extent. In spite of the extensive changes in the gastrointestinal tract, clinical symptoms referable to them are surprisingly few and consist of diarrhea alternating with constipation, sometimes bloody stools, occasionally intussusception, and emaciation. There are no specific changes in the blood.

LYMPHOSARCOMA

Kundrat, who first described the disease lymphosarcomatosis, defined the unit of growth as a malignant tumor of lymph nodes or of other lymphoid structures in which lymphocytes proliferate diffusely in an inconspicuous stroma of connective tissue. He predicated a tendency on the part of the process to confine itself within more or less sharply defined limits, but noted its proclivity to expand locally and often ruthlessly. In 17 cases of lymphosarcoma encoun-

tered among 11,925 necropsies at Bellevue Hospital, 9 illustrated rather faithfully Kundrat's maxim of local growth; in the remaining 8 there appeared to be little, if any, inclination to spare tissues, regionally or otherwise, but there was a degree of territorial expansion seldom distanced by any of the other lymphoid diseases.

In a series of 100 cases recorded by Kundrat, Ghon and Roman, MacCallum and myself,[20] lymphosarcoma occurred preponderantly in the following situations: gastrointestinal tract, 36 cases; thymic remains, 21; cervical nodes, 14; abdominal nodes, 11; pharynx, 7; tonsils, 3; mouth, 2; inguinal nodes, 2; spleen, 1; axillary nodes, 1; thoracic nodes, 1; prostate, 1. In other words, the tissues of the deeper lymphoid structures were preponderantly or "primarily" concerned in 70 of the 100 cases, including, in the order of their frequency, the gastrointestinal tract, thymus, abdominal lymph nodes, spleen and thoracic nodes. Of the remaining 30 cases, the cervical nodes were preponderantly or "primarily" involved in 14, the causative agent entering, no doubt, through the upper part of the gastrointestinal tract by way of the faucial tonsils. In 12 of the remaining 16 cases, the condition involved superficial structures belonging to the gastrointestinal tract, including the pharynx, tonsils and mouth, and in the other 4 the inguinal and axillary nodes and the prostate were preponderantly or "primarily" involved.

In those comparatively rare cases of lymphosarcoma in which the lymph follicles are not completely obliterated, the lymphocytes which lie in immediate proximity to the germinal centers are slightly larger than the familiar small lymphocytes and their nuclei are finely stippled. In one group of cases this type of lymphocyte retains its structure throughout and infiltrates the substance and capsule of the node to form a so-called large cell lymphosarcoma. In a second group of cases the prevailing lymphocyte is noticeably smaller and its nucleus is densely packed and almost completely fills the body of the cell. This is the type of cell which proliferates to form a so-called small cell lymphosarcoma. A third type of "lymphosarcoma" has been described under the title of "reticulum cell lymphosarcoma." It is supposed to be capable of arising from reticulum cells both in the germinal centers of the lymph follicles and in the parenchyma of the node, but in view of the fact that the relationship of the reticulum cell, if any, to the lymphocyte is not known, it would seem advisable to designate the tumor in question a reticulum cell sarcoma of lymph nodes.

20. Symmers, D.: Am. J. M. Sc. **174**:9, 1927.

Much the same statement applies to the polymorphous cell sarcoma of lymph nodes. This tumor results from direct transformation of the germinal centers in the follicles of giant follicular lymphadenopathy, and the nature of the several cell types in it is not known.

CONCLUSIONS

Anatomically, chronic lymphogenous leukemia is broadly divisible into two forms, a splenomegalic form, in which lymphoid hyperplasia is preponderant or "primary" in the spleen, and a form in which the abdominal lymph nodes or the abdominal and thoracic nodes combined are preponderantly or "primarily" enlarged. In both forms enlargement of the superficial nodes, if it occurs at all, is secondary. The same statement applies to Hodgkin's disease, with the addition that in this disease there is a form that is preponderant or "primary" in the thymus and one that is preponderant or "primary" in the liver. In giant follicular lymphadenopathy the preponderant or "primary" changes are most often in the lymph nodes of the abdomen. It is probable that there is a preponderant or "primary" splenomegalic form, but proof of this awaits confirmation by evidence adduced at necropsy. In the majority of all cases of lymphosarcoma (70 per cent) the preponderant changes are in the gastrointestinal tract, in the thymus or in the abdominal or the thoracic lymph nodes; rarely, in the spleen. Enlargement of the superficial lymph nodes, if it occurs at all, is usually a later and secondary feature. The gastrointestinal so-called "pseudoleukemia" of Briquet, as its name implies, is preponderantly or "primarily" a disease of the lymphoid tissues of the gastrointestinal tract. Splenomegaly and enlargement of the superficial and deep lymph nodes, while almost constantly present, are secondary features.

The distribution of the lesions in the lymph nodes of the thorax and abdomen seems to warrant the view that the causative agent of each of the lymphoid diseases enters through mucous membranes, most often through the mucous membrane of the gastrointestinal tract. In other circumstances, it appears that the causative agent filters through both the mucosal follicles and the lymph nodes in the abdomen and chest and eventually brings about hyperplastic changes in the follicles of the spleen, in the thymus or its remains or in the auxiliary lymphoid foci scattered through the interstitial tissues of various organs.

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EFFECT OF ADMINISTRATION OF DIGITALIS ON COAGULABILITY OF HUMAN BLOOD

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ST. LOUIS

Several investigators recently have reported that the administration of digitalis to animals causes a decrease in the clotting time of blood. Tanaka [1] noted an acceleration of coagulation when strophanthin was given intravenously to rabbits; the drug in vitro was without effect. During the past year Macht [2] in a group of experiments concerning the influence of heparin on the toxicity of digitaloids discovered that administration of heparin to cats prior to intravenous injection of solutions of ouabain and digitalis significantly lowered the toxicity of these drugs. In addition, he found that the various digitaloids when added to shed blood in vitro hastened coagulation. Shortly thereafter Werch [3] pointed out that a significant reduction of the coagulation time resulted when digitalis was given intravenously to rabbits. The present study was carried out in order to determine whether therapeutic doses of digitalis would similarly affect the coagulation time in man.

METHOD OF STUDY

Thirty-five patients of both sexes from 24 to 78 years of age, with and without involvement of the heart, some with cardiac failure and others without disease, were followed with repeated determinations of the blood coagulation time. In addition, frequent determinations of the prothrombin time by the Smith bedside method [4] and observations on clot retraction were made in about half the cases. For 24 of the patients the clotting time was determined during an initial control period varying from two to fourteen days (average of four days), then during a period of administration of digitalis which lasted from three to ten days (average five and nine tenths days) and subsequently for two to twelve days (average of six and two-tenths days) after use of the drug was stopped. The digitalizing dose [5] varied from 0.9 to 2.6 Gm., with an average of 1.6 Gm. In every case the drug was given orally. Of the other 11 subjects studied, 7 received no digitalis at any time, while 4 were patients who had been and continued to be given a maintenance dosage of digitalis. Approximately one third of all the patients were ambulatory; the remainder were confined to the hospital at partial or complete rest in bed.

The Lee-White method [6] was used for the determinations of clotting time. Blood was collected in a 5 cc. syringe, which was rinsed with isotonic solution of sodium chloride and shaken as dry as possible just before it was used. The tubes were 8 mm. in diameter, and 19 gage needles were employed. Five cubic centimeters of blood was withdrawn from one of the antecubital veins, and 1 cc. was immediately placed in each of three tubes. These tubes were permitted to stand undisturbed for five minutes, and then the first tube was tipped gently every half-minute until clotting took place. The second tube was then tipped until it clotted. The third tube, which had not been disturbed, usually showed clotting soon after the second. The time at which the blood in the third tube clotted was considered the final reading.

The actual procedures of the tests were always carried out by two observers in order to facilitate the performance of the tests. One person watched the various tubes continuously in order to determine the end point more exactly, whereas the other worker performed the venesections. After the tests on the first 14 patients a different investigator performed the remainder of the venesections, for the last 10 patients. For this reason it was considered advisable to separate the entire experimental group into two series of patients, series 1 and 2. It will be noted that the results obtained in the two series were comparable.

RESULTS

The coagulability of the blood was found to be accelerated in each of the 24 patients during the active period of digitalization. The average of all the readings (series 1 and 2) during the control period was 16.1 minutes, whereas during

From the Department of Internal Medicine, Washington University Medical School, Barnes Hospital and the Washington University Clinics.

1. Tanaka, H.: Ueber den Einfluss des Strophanthins auf die Gerinnbarkeit des Blutes, Okayama-Igakkai-Zasshi **40**:1826 (Sept.) 1928.

2. Macht, D. I.: Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs, Ann. Int. Med. **18**:772-791 (May) 1943.

3. Werch, S. C.: Reduction of the Coagulation Time of Rabbit's Blood by Digitalis, Quart. Bull., Northwestern Univ. M. School **17**:50-51, 1943.

4. Zeffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanisms at Low Prothrombin Levels, Proc. Soc. Exper. Biol. & Med. **40**:595-597 (April) 1939.

5. U. S. P. XII digitalis was used in this study.

6. Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of Blood, Am. J. M. Sc. **145**: 495-503 (April) 1913.

digitalization it was 12.8 minutes, an average decrease of 3.3 minutes. The individual differences, studied statistically by the Fisher t test, were found to be highly significant. Table 1 shows a comparison of the average clotting time before and during administration of digitalis for the 24 patients of series 1 and 2. The average decrease of the clotting time of series 1 during digitalization was 3.7 minutes (variation 0.4 to 6.2), and that of series 2 was 2.6 minutes (variation 1.0 to 4.7). Chart 1 illustrates graphically the decrease in the clotting time during digitalis administration in a 54 year old man with myxedema and a normally functioning cardiovascular system. Chart 2 presents a similar curve for a 42 year old woman with hypertension and cardiac decompensation. One of the most striking effects on the coagulation time occurred in a man aged 59 with hypertension, disease of the coronary arteries and paroxysmal nocturnal dyspnea (chart 3).

TABLE 1.—*Comparison of Average Clotting Times of Series 1 and 2 Before and During Administration of Digitalis*

Patient No.	Time, Minutes		
	Before	During	Difference
	Series 1 *		
1	14.3	11.4	2.9
2	18.0	13.5	4.5
3	15.0	11.5	3.5
4	15.4	15.0	0.4
5	20.7	17.7	3.0
6	17.3	15.6	1.7
7	17.7	15.4	2.3
8	19.0	12.8	6.2
9	19.8	15.0	4.8
10	20.8	15.3	5.5
11	16.5	12.2	4.3
12	16.0	12.6	3.4
13	19.0	12.9	6.1
14	14.0	10.0	4.0
Averages	17.4	13.6	3.7
	Series 2 †		
15	14.4	10.7	3.7
16	13.5	10.6	2.9
17	13.1	10.1	3.0
18	14.0	9.3	4.7
19	16.3	13.3	3.0
20	13.9	12.6	1.3
21	13.8	12.4	1.4
22	15.9	12.0	3.9
23	13.9	12.5	1.4
24	14.3	13.3	1.0
Averages	14.3	11.7	2.6
	Series 1 and 2 Combined ‡		
Average	16.1	12.8	3.3

* Standard deviation = 1.67
Standard error = 0.45
t = 8.3 ** (highly significant).
† Standard deviation = 1.44
Standard error = 0.45
t = 5.8 ** (highly significant).
‡ Standard deviation = 1.54
Standard error = 0.314
t = 10.44 ** (highly significant).

In 13 cases a study was made of the differences between the clotting times determined during and after administration of digitalis. Comparison of the average coagulation times obtained during administration of digitalis with those obtained after the drug was stopped revealed an increase of 1.2 minutes following cessation of the medication, representing an average change from 13.6 to 14.8 minutes. These differences were also found to be significant statistically by the Fisher t test. It should be pointed out, however, that the digitalis had not yet been completely excreted from the body during the period of this study and that it is likely that prolongation of this observation would show greater changes as the drug was completely removed from the body. Table 2 shows the average clotting times during and after administration of

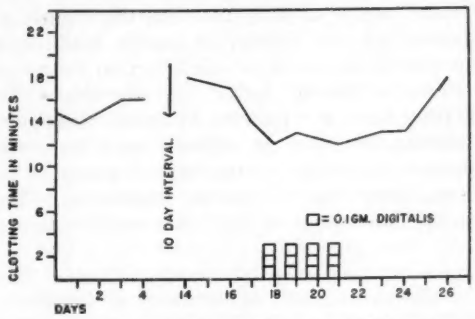

Chart 1 (patient 12).—Effect of administration of digitalis on the clotting time.

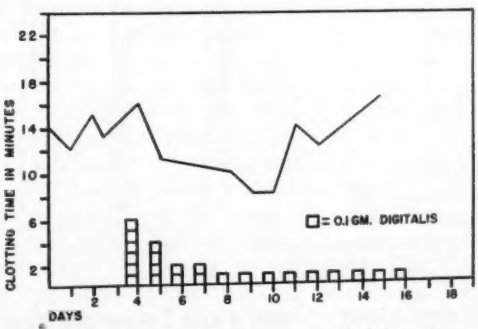

Chart 2 (patient 17).—Effect of administration of digitalis on the clotting time.

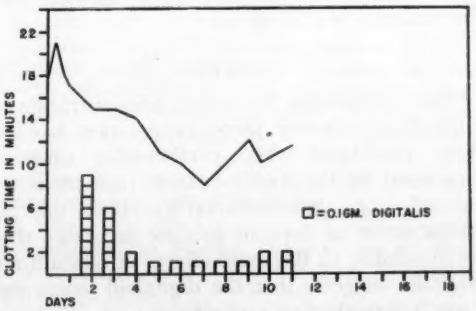

Chart 3 (patient 13).—Effect of administration of digitalis on the clotting time.

digitalis, and chart 1 illustrates these readings for patient 12.

Studies on prothrombin time before, during and after digitalization revealed no significant difference in any of the subjects studied. In addition, no change in clot retraction was observed. The presence or absence of heart failure, degree of drug reaction, therapeutic response, age, sex, activity or specific condition of the patient had no detectable effect on the coagulation-accelerating action of digitalis. The clotting times of 4 patients who were being given maintenance doses of digitalis were somewhat shorter than those of the control group of patients, receiving no specific medication. This group, however, is so small that conclusions may not be drawn. Charts 4 and 5 show graphically the trend of the individual values for coagulation time of 2 control patients to whom no digitalis was administered. No untoward reactions were encountered in this study.

TABLE 2.—*Comparison of Average Clotting Times During and After Administration of Digitalis*

Patient No.	Time, Minutes During	After	Difference
2	13.5	13.8	0.3
3	11.5	17.9	6.4
4	15.0	18.2	3.2
5	17.7	15.7	—2.0
6	15.6	14.6	—1.0
8	12.7	18.0	5.3
9	15.0	15.2	0.2
10	15.3	15.5	0.2
11	12.2	14.0	1.8
12	12.7	13.7	1.0
14	10.0	11.5	1.5
19	13.2	13.1	—0.1
23	12.5	11.7	—0.8
Averages	13.6	14.8	1.2

Standard deviation = 2.12
Standard error = 0.59
t = 2.03 * (significant).

COMMENT

The mechanism by which administration of digitalis accelerates blood coagulation has not been elucidated. The prothrombin time, as measured by the Smith bedside method, is not altered. The demonstration by Macht that administration of heparin to cats decreases their susceptibility to the toxic effects of ouabain and digitalis suggests that the digitaloid drugs may have a thromboplastic effect.

The clinical importance of these observations is only suggestive at this time. It is entirely possible that the increase in clotting propensity of blood induced by digitalis may result in a predisposition to thrombotic or embolic phenomena. Certainly thrombosis and embolism are known to occur in patients who are being digitalized. Frequently other factors are present which may cause these complications, but the possibility that administration of digitalis may favor their development must unquestionably be considered.

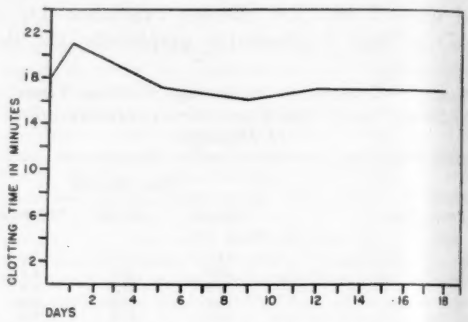

Chart 4 (control 3).—Variation in the clotting time of a control patient.

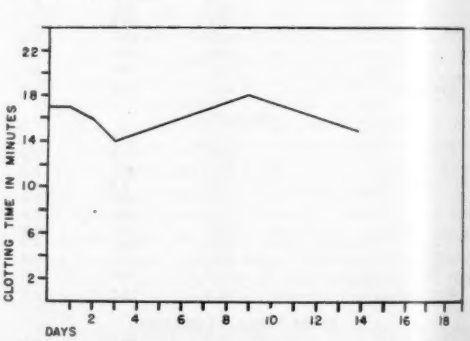

Chart 5 (control 5).—Variation in the clotting time of a control patient.

SUMMARY

Therapeutic doses of digitalis caused the clotting time to be accelerated in each of 24 patients during the period of administration of the drug. After the administration of digitalis was discontinued, the coagulation time increased in the majority of 13 patients so studied, even though the drug had not yet been completely excreted during the period of observation.

No changes were observed in clot retraction and in prothrombin time. It is suggested that digitaloid drugs may have a thromboplastic effect on the clotting mechanism.

USE OF FLUORESCEIN METHOD IN ESTABLISHMENT OF DIAGNOSIS AND PROGNOSIS OF PERIPHERAL VASCULAR DISEASES

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NEW YORK

Some time ago Lange and Boyd [1] showed that intravenously injected fluorescein can be made visible immediately on its arrival in the small blood vessels of the skin and the mucous membranes if a beam of long wave ultraviolet radiation is directed on a given area in a dark room. On this basic principle it seemed that the procedure might aid in establishing the diagnosis and prognosis of peripheral vascular diseases. Certain conditions, however, had to be studied before the test could be introduced for general use in various problems concerning vascularity of tissues.

TABLE 1.—*Fluorophotometric Readings of Fluorescein Solutions*

Concentration	Fluorescein with Sodium Bicarbonate p_H 5.7 Fluorescence	Sodium Fluorescein * p_H 5.7 Fluorescence
1:500,000	100	78
1:1,000,000	56	44
1:5,000,000	14	11

* The concentration of sodium fluorescein is figured on the basis of the content of fluorescein.

PHYSICAL AND PHARMACOLOGIC BASIS

Fluorescein is resorcinolphthalein. It has an extremely small molecule, since its molecular weight is 332. It is a brown substance which is soluble in an alkaline solution. While the sodium salt is freely soluble in water, it is optically much less active than fluorescein (table 1). Accordingly, it is inadvisable to use sodium fluorescein for actual tests, since more is required to obtain an optical effect equal to that of fluorescein. Fluorescein is not radiopaque, but it fluoresces, i. e., it absorbs ultraviolet rays of a certain wavelength and converts them instantaneously into longer wavelengths in the yellow-green region of the spectrum.

Aided by a Grant from the John and Mary R. Markle Foundation.

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and the Metropolitan Hospital (Research Unit).

Originally Ehrlich [2] used the dye to investigate the secretion of the aqueous humor in the rabbit's eye, its flow through the eye (Ehrlich's line) and its absorption. This basic work started extensive studies on this special ophthalmologic question, and valuable observations on capillary permeability in the eye have been made.[3] Koch [4] introduced a method for objective determination of the circulation time by injecting fluorescein into a vein of one arm and drawing samples of blood from a vein of the other arm and examining the samples in full daylight for the first appearance of fluorescence, Ellinger and Hirth [5] were the first to observe the dye in the organs of frogs. They injected it into the lymph sac and noted its appearance in the renal glomeruli and studied the excretory mechanism involved. Lange and Wollheim [6] showed that the dye can be seen in the capillaries of the lip when a proper source of light is used. Lange and Boyd [7] demonstrated that properly filtered and intense long wave ultraviolet radiation caused the dye to become visible wherever the rays could penetrate, i. e., in the skin, the mucous membranes or any organ properly exposed.

1. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**:934-952, 1942.

2. Ehrlich, P.: Ueber provocierte Fluorescenzerscheinungen am Auge, Deutsche med. Wchnschr. **8**: 35-37, 1882.

3. Hertel, E.: Ueber die Bedeutung der Ehrlichschen Fluoresceinversuche, Arch. f. Augenh. **100-101**: 460-469, 1929. Gifford, H.: Use of Fluorescein Intravenously as an Aid to Ophthalmic Diagnosis and Treatment, Arch. Ophth. **24**:122-131 (July) 1940. Ehrlich.[2]

4. Koch, E.: Velocity of Blood Stream, Deutsches Arch. f. klin. Med. **140**:39-66, 1922.

5. Ellinger, P., and Hirth, A.: Mikroskopische Untersuchungen an lebenden Organen; zur Funktion der Froschniere, Arch. f. exper. Path. u. Pharmakol. **145**:193-210, 1929.

6. Lange, K., and Wollheim, E.: Die Kreislaufzeit und ihre Beziehung zu anderen Kreislaufgrössen, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1931, Kong. 43, pp. 134-140.

7. Lange, K., and Boyd, L. J.: The Technique of the Fluorescein Test to Determine the Adequacy of Circulation in Peripheral Vascular Diseases, the Circulation Time and Capillary Permeability, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **6**:78-81, 1934.

Fluorescein is most fluorescent at a wavelength of 3,600 angstrom units. This is just at the borderline between visible light and ultraviolet rays which do not cause an erythema. The transmission characteristics of a filter which gives optimal results are shown in chart 1.

A mercury vapor bulb of the flood or spot type (EH_4 or CH_4) of the General Electric Company is used for generating the ultraviolet rays. On its surface a double filter of the aforementioned characteristics is mounted. The entire unit is inexpensive, portable and easy to handle.[8] The fluorescence of fluorescein is also excited by rays of somewhat longer wavelength, that is, about 4,000 angstrom units. This blue light, however, is clearly visible and obscures entirely the golden green light emitted by the dye. Therefore it is necessary for the observer to wear yellow glasses, which eliminate the blue and transmit only the yellow-green of the fluorescein. Since this system can be worked with an ordinary incandescent lamp, it is used for photoelectric measurements with the Dermofluorometer,[9] while the ultraviolet ray source is used throughout for visual observation.

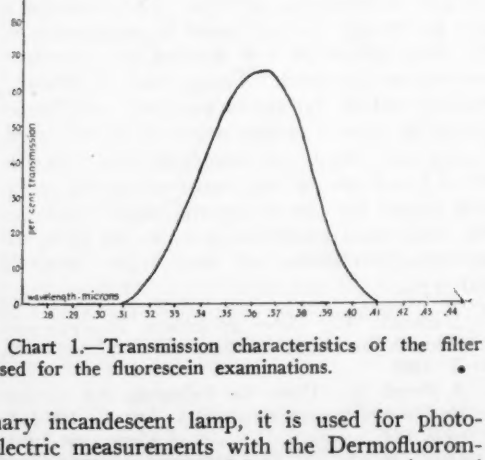
ERYTHEMAL
NEAR ULTRAVIOLET
VISIBLE VIOLET
per cent transmission
wavelength-microns
.28 .29 .30 .31 .32 .33 .34 .35 .36 .37 .38 .39 .40 .41 .42 .43 .44

Chart 1.—Transmission characteristics of the filter used for the fluorescein examinations.

The Dermofluorometer [10] works on the following basic principle: A small but powerful incandescent light is rigidly alined at an angle of 90 degrees to a phototube; by a bakelite plate both are kept at a constant distance from the skin of the patient to be observed. A blue filter in front of the source of light transmits rays mainly in the region of 4,000 angstrom units, and the phototube, which picks up the yellow-green emitted by the fluorescein carries a yellow filter to prevent the blue from impinging on the phototube, so that it picks up only the change in color produced by the intravenously injected fluorescein. A reading before the injection gives a basic value, which usually is very small; later it is deducted from the values obtained after the injection.

The current originating in the phototube is then amplified three hundred thousand times, and the result is read from a microammeter. The device is calibrated so that an alkaline fluorescein solution of a concentration of 1:30,000,000 in a cuvette of a depth of 5 mm. causes a deflection of one division. This is called 1 fluorescein skin unit. The Dermofluorometer is not necessary for passing a judgment in cases of peripheral vascular diseases; it is merely a refinement. But it is necessary for studies of capillary permeability and for completely objective determinations of the circulation time to any part of the body surface. Visual observation remains the method of choice for peripheral vascular diseases.

Fluorescein is not toxic in the dosage used. Up to the present we have examined over 1,000 patients with this method and have had no toxic reaction, although 11 of our patients vomited or retched once during or immediately following the injection. No other sensation occurred, and the tests were continued as usual. This brief nausea seems to be due to an individual sensitivity of the center, for 1 patient had vomiting each time the test was repeated, four times in all, and even after the injection of only 4 cc. In experiments on animals a dose of 0.3 cc. of the 5 per cent solution given intraperitoneally to 20 Gm. mice killed 5 out of a litter of 10 mice within six hours; the rest survived. This dose is enormous as compared with the doses given to patients. We were unable to kill a rabbit with 5 per cent fluorescein solution unless the same amount of isotonic solution of sodium chloride alone also killed an animal of the same size.

Fluorescein does not acquire any photodynamic activity as long as serum is protecting the red corpuscles. The interesting observations of Blum [11] on the photodynamic action of fluorescein causing hemolysis were all made on washed corpuscles. We were not able to produce a hemolysis in vitro when we exposed a 1:10,000 solution of fluorescein in whole blood to full sunlight for six hours.

The substance is excreted completely and without chemical change in the urine. This excretion seems to be a purely glomerular function. The duration of the excretion varies according

8. Supplied by the George W. Gates Co., Franklin Square, L. I.

9. Manufactured for us by the Photovolt Corporation, New York, N. Y.

10. Lange, K., and Krewer, S. E.: The Dermofluorometer, J. Lab. & Clin. Med. **28**:1746-1750, 1943.

11. Blum, H. F.: Studies of Photodynamic Action, Biol. Bull. **58**:224-237, 1930.

to the amount given and the glomerular function. A normal person excretes the usual dose within sixteen to thirty hours. Persons with severe renal damage may require sixty hours for excretion of the dye. We have repeated injections as often as seven times within three weeks without any ill effect. We also have reinjected the full dose within twenty-four hours without any undesired effects.

On reaching a capillary the dye diffuses immediately through the wall of the vessel into the interstitial spaces, where it can easily be observed under the capillary microscope. It diffuses over the entire length of the capillary, and no variation can be observed in diffusion in different parts of the vessel, as was described by Rous, Gilding and Smith [12] for other dyes. No living vascularized tissue observed up to the present remains unstained by the dye. The degree of staining differs; apparently it depends on the physiologic capillary permeability, which may differ greatly from organ to organ.

Dead tissue cells do not stain even if the blood supply in the area is fully preserved, as Friedemann [13] suggested without elaborating on it. In order to prove this fact a loop of small intestine of a rabbit under pentobarbital sodium anesthesia was strangulated by means of a rubber band and then dipped into a 5 per cent sodium cyanide solution for three minutes. After this period the band was released and fluorescein injected into a vein of the ear. The entire small intestine displayed an intense fluorescence with the exception of those parts which were previously dipped into the cyanide solution. They remained purple although the blood vessels leading into this area exhibited full fluorescence. No fluorescence could be noticed in this tissue even after forty-five minutes. Tissue cells killed by anoxia alone show the same lack of fluorescence.

Fluorescein is adsorbed on the plasma proteins to the extent of about 40 per cent of the total amount present. It seemed of interest to know whether physiologic or pathologic changes in plasma proteins would influence the staining when higher adsorption of part of the dye occurred in persons with high plasma proteins.

Plasma of patients was concentrated by ultrafiltration or diluted by isotonic solution of sodium chloride to obtain variations within pathologic range. Fluorescein was added to the different plasma protein concentrations in equal amounts, and the specimens were subjected to ultrafiltration according to the method of Bechhold,[14] collodion U. S. P. being used for the membrane. The same filter was used for all filtrations which were carried out at a constant suction, 60 mm. of mercury. The filtrate and the supernatant fluid were then examined for their fluorescein content by the fluorophotometer. The data obtained prove that variations of the plasma proteins within the pathologic range do not influence the amount of fluorescein immediately available for diffusion into the tissue (table 2).

TABLE 2.—*Ultrafiltrations of a Fluorescein Solution 1: 1,000,000 in Plasmas with Various Protein Contents*

	Protein, per Cent		
	11.0	6.9	2.5
Amount of filtration per minute, cc.	0.066	0.083	0.090
Concentration of filtrate	1:2,500,000	1:2,500,000	1:2,400,000
Concentration of supernatent after 2 cc. was filtered off	1:870,000	1:850,000	1:840,000

It is generally accepted that capillary filtration is a mere ultrafiltration. The physiologic basis of increased fluorescence in the tissue can thus be cleared in ultrafiltration experiments, and the following questions were therefore investigated by means of such experiments:

1. Does the intracapillary pressure change the concentration of fluorescein in the filtrate providing the membrane does not change its permeability? Table 3 demonstrates that changes of pressure influence only the amount of fluids passing through the filter and that the concentration of fluorescein in the filtrate remains constant.

TABLE 3.—*Ultrafiltration of a 1: 250,000 Solution of Fluorescein in Plasma (Total Protein Content 6.8 per Cent)*

Suction, Mm. Hg	Amount Filtered in 15 Min., Cc.	Concentration of Filtrate
—60	1.9	1:475,000
—45	1.2	1:455,000
—30	0.7	1:455,000
—20	0.4	1:440,000

2. Does a change in permeability of the membrane represented by a dilution of the collodion for the production of the membrane change the concentration of the filtrate or the amount of filtrate only? Table 4 shows that a change in permeability of the filter at equal pressure

12. Rous, P.; Gilding, H. P., and Smith, F.: The Gradient of Vascular Permeability, J. Exper. Med. 51:807-830, 1930.

13. Friedemann, U., in Oppenheimer, C.: Handbuch der Biochemie des Menschen, Jena, G. Fischer, 1909, vol. 3, pt. 2, p. 282.

14. Bechhold, J. H., in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenburg, 1921-1925, sect. 3, pt. 3, no. 3, pp. 583-594.

changes the concentration of the filtrate as well as the amount per minute.

It should be understood, however, that fluorescein, like all crystaloids, diffuses independently of the water since it depends on its own partial pressure. Water may be drawn *out* of the tissue while fluorescein is diffusing *into* the tissue owing to differences in partial pressure. One is therefore in these tests *not* working with "labeled water." The diffusion depends only on the intracapillary pressure and the status of the capillary membrane.

The reaction to the fluorescein test is definitely disturbed if the skin is pigmented abnormally. Colored people cannot be examined for intensity of staining. However, amputation levels can be clearly determined, since the skin of these people usually has poorly pigmented areas, which become clearly visible under ultraviolet rays, that is, assume a greenish brown tint after the injection of fluorescein. Determinations of circulation time to the legs in colored people were carried out with the Dermofluorometer attached to the

TABLE 4.—*Fluorescein Solution (1: 500,000) Filtered Through Different Ultrafilters*

	Ultrafilter Prepared with Collodion U. S. P., Suction —60 Mm. Hg	Ultrafilter Prepared with 50% Collodion and 50% Ether, Suction —60 Mm. Hg
Amount of filtrate in 30 minutes	4.8 cc.	7.0 cc.
Fluorescein concentration in filtrate	1:1,440,000	1:680,000

soles. Sun-tanned skin of white persons may also be a source of error. Before certain areas are used for Dermofluorometer readings they should be carefully examined to make sure they are free of collections of pigment deposits.

PHYSIOLOGIC BASIS

Inflammation.—After the basic facts of diffusion were obtained by the ultrafiltration experiments the changes occurring in the fluorescence of inflamed tissues after an injection of the dye could be more clearly estimated. Even the slightest degree of inflammation anywhere in the skin or mucous membranes leads immediately after the injection of the dye to a pronounced hyperfluorescence in this area. For the most part, this hyperfluorescence does not result from increased capillary dilatation or from inclusion of more capillaries into the rapid circulation but consists mainly of increased capillary permeability. This can easily be demonstrated by pressing a glass spatula on such an inflamed area to empty the capillaries. An inflamed area retains its marked hyperfluorescence as compared with a normal area treated similarly, which indicates that more dye has penetrated into the interstitial spaces. The removal of the dye from an inflamed area takes much longer than from a normal area. After the skin is entirely free of fluorescence an inflamed area can still retain an intense glow. Whether this can be explained by lymphatic blockage, as described by Menkin,[15] is subject to further investigation. The outstanding fact, however, is that even the slightest inflammation immediately leads apparently to a strong increase in capillary permeability.

Intracutaneous injections of histamine evoke a similar picture, as might be expected. The hyperfluorescent histamine wheal, however, disappears as quickly as the fluorescence in the rest of the skin; moreover, the area irritated by histamine clears of fluorescein rapidly, in contrast to one really inflamed.

Scratching the skin with a blunt instrument after a previous injection of the dye gives a double response. Immediately afterward the area of the stroke shows greatly decreased fluorescence for about ninety seconds, apparently as a result of capillary contraction. Then the band of fluorescence gradually increases so that it is much wider than the original stroke, and it stays hyperfluorescent under the pressure of a glass spatula. This indicates that there is not only capillary dilatation but a considerable increase in capillary permeability; this happened in every case (16 persons) irrespective of the appearance of visible local edema. In persons with marked dermographism the reaction is stronger and the hyperfluorescent band wider, but the response is not different in principle.

Intensity of Staining Dependent on Blood Supply.—Since the test was intended for examination of persons with peripheral vascular diseases it was necessary to observe whether the intensity of staining in general depends on the amount of blood supply to a limb per minute. In 3 cases a blood pressure cuff was applied to one thigh and inflated to a pressure between the systolic and the diastolic level. Fluorescein in the normal doses was then injected intravenously, and the staining of the legs was observed visually and instrumentally. It was immediately evident that the leg the arteries of which were partly occluded stained much less than the leg with normal circulation. The objective readings obtained with the Dermofluorometer are shown in chart 2. To avoid error from an increased bluish discoloration of the congested leg, which would influence the readings, the test was first performed without fluorescein and the colorimetric changes

15. Menkin, V.: Mechanism of Inflammation, Arch. Path. **24**:65-82 (July) 1937.

noted. These values were then deducted from the actual readings in the fluorescein test. The results proved clearly that the staining of the skin of a leg depends on its blood supply. To avoid the factor of venous congestion, the test was repeated with simple obstruction of the femoral artery by an instrument which compressed the artery with an adjustable intensity in the groin. The result was the same as in the cuff test. The circulation time to any part of

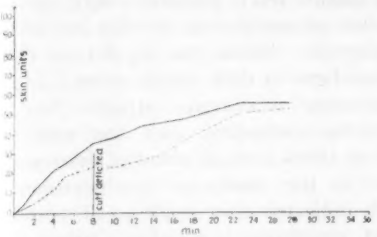

Chart 2.—Dermofluorometer curves indicating the diminished staining in a leg with artificially diminished blood supply. The broken line shows the readings obtained on the leg with a blood pressure cuff around the thigh inflated to a pressure between the systolic and the diastolic blood pressure.

the body can be determined objectively with this method. The method and results of this test have been discussed at length elsewhere.[16] A few basic facts, however, should be repeated. The appropriate place for determination of the normal circulation time with the fluorescein

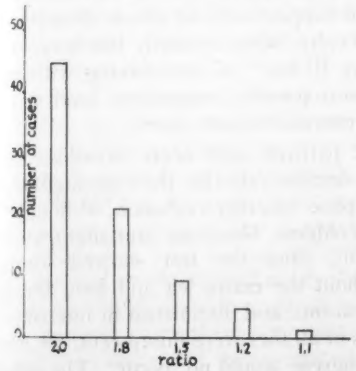

Chart 3.—Ratio between the arm-leg and the arm-lip circulation time in normal persons.

method is the lips. The arm-lip time of a normal person is fifteen to twenty seconds; most persons have values ranging between fifteen and seventeen and a half seconds (216 cases). There is a definite trend toward longer circulation time with increasing age. Seventy-one normal persons were examined in respect to circulation time to their legs. The Dermofluorometer was attached by a usual rubber strap to the outside of the calf two hands below the knee for all white patients; for the colored people it was attached to the sole of the foot. In 92.5 per cent of the cases the arm to leg time did not exceed twice the arm to lip time—a ratio for the arm-leg to arm-lip time of 2 or less. This relation seems maintained constantly. The fastest flow to the legs observed in normal persons gave a ratio of 1.3 between arm-leg and arm-lip time. Chart 3 gives the different ratios between arm-lip and arm-leg time in normal subjects. Incidentally, by comparing the color of the subject's skin with that of the observer or his assistant, one can observe with an accuracy of a few seconds the first appearance of the dye in any cutaneous surface by visual observation without recourse to the Dermofluorometer.

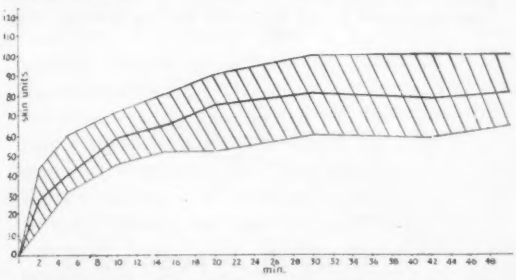

Chart 4.—The upper and lower limits and the average of staining as measured by the Dermofluorometer on the legs of 20 normal persons.

Since staining of the skin depends on the amount of blood reaching an area per time unit, provided capillary permeability is normal, fluorescence curves of the different areas of normal persons could be established. Charts 4 and 5 represent such a curve of average values as read on the legs and feet of 20 normal persons and give the upper and lower limits. Obviously patients with a gross disturbance of blood supply to a limb would have an abnormal type of curve.

CLINICAL EVIDENCE

Method.—All patients were examined after they had rested for at least fifteen minutes with the extremities exposed to room temperature. The room temperature should range between 74 and 80 F. Exposure to cold definitely changes the fluorescence of the skin by decreasing capillary permeability.[17] All tests were carried out in a dark room. For visual observation the mercury

16. Lange, K., and Boyd, L. J.: Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), Am. J. M. Sc. **206**:438-448, 1943.

17. Lange, K.: The Effect of Cold on Capillary Permeability, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **5**:154-162, 1942.

vapor lamps were used, while photoelectric determinations were made with the Dermofluorometer. The patient's skin was observed before the test and compared with the skin of the observer or of an assistant under the long wave ultraviolet radiation. Basic Dermofluorometer readings were taken on all pertinent areas which were to be measured later, and the low values were noted. If a patient had had an ointment applied to his skin, great care was taken to remove it completely, since most ointments have a whitish fluorescence of their own. If an ulcer was covered with slough, the latter had to be removed, for it would have entirely obscured the fluorescence of the underlying capillaries. Wet saline dressings applied for twelve to twenty-four hours were often helpful. After these preparations the patient received an intravenous injection of 1.3 cc. per 10 Kg. of body weight of the 5 per cent fluorescein solution to which 5 per cent sodium bicarbonate had been added to render it soluble.[18] The first 4 cc. of the solution was given as rapidly as a 20 gage needle permitted. The rest was given slowly, so that the total amount was injected in ninety seconds. The ultraviolet ray lamp was directed to the patient's lips to permit observation of arm-lip time, while the Dermofluorometer, if used, was attached to the leg. The sudden appearance of full fluorescence in the lip is called the end point, while the initial deflection of the Dermofluorometer pointer is the end point for the arm-leg time.

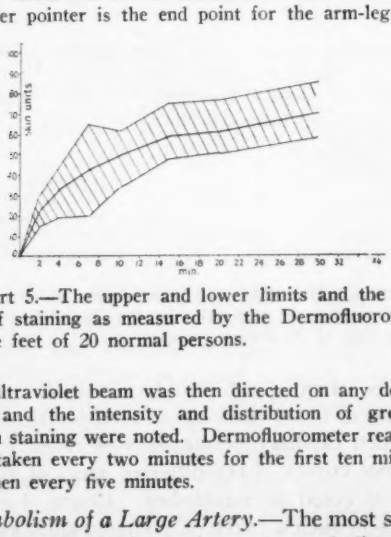

Chart 5.—The upper and lower limits and the average of staining as measured by the Dermofluorometer on the feet of 20 normal persons.

The ultraviolet beam was then directed on any desired area, and the intensity and distribution of greenish golden staining were noted. Dermofluorometer readings were taken every two minutes for the first ten minutes and then every five minutes.

Embolism of a Large Artery.—The most striking picture is obtained when acute embolism has taken place in a limb with little or no previous arteriosclerosis. We have observed 9 instances of this. In 4 the embolus arose from a mitral stenosis, while auricular fibrillation was the cause for the embolus in 4 others. Subacute bacterial endocarditis was provocative in 1. In 5 the embolus lodged in the popliteal artery, while it occurred at the iliac bifurcation in the others. In 1 case embolism was repeated three days after the first episode. Both accidents were successfully treated by embolectomy. This case was recently described by Lesser.[19]

18. Supplied in ampules by the C. F. Kirck Company, New York, N. Y.

In all but 2 cases fluorescein permitted us to establish exactly the level of blood supply in the skin. One to two minutes after the injection, but most clearly after ten minutes, there is a sharp line of demarcation where normal fluorescence stops. This was followed in 5 cases by a hyperfluorescent line which extended for about 1 cm. distally in which maximal capillary dilatation with increased capillary permeability apparently had taken place (positive reaction to a glass spatula test), probably owing to the accumulation of metabolites in this borderline area of gangrene. Below, the leg did not change its original light to dark purple color. The line of demarcation was never straight but showed peninsulas extending into the nonfluorescent area; at times a small island of fluorescence was noted in the otherwise nonfluorescent tissue, which indicated that some small vessels maintained circulation somewhat farther than the bulk of the patent vessels.

In 5 cases a block of the sympathetic chain from the second to the fourth lumbar segment was performed immediately after the fluorescein test in order to exclude vasospasm as a factor contributing to the complete inhibition of blood flow. In 1 of these cases the borderline of fluorescence slowly crept distally twelve minutes after the spinal block. This indicated either that vascular relaxation permitted the embolus to move or that collateral vessels previously in complete spasm had relaxed and taken over part of the blood supply. In 7 cases the lowest level of blood supply could be clearly determined, and the difficulty, which recently has been reemphasized by Bickel,[20] of determining with certainty the lowest possible amputation level can be entirely removed in such cases.

In 2 patients with acute embolism we were able to demonstrate that the embolus had not led to complete vascular occlusion, although it produced coldness, blanching and slight mottling of the skin, since the test showed fluorescence throughout the entire leg and foot, but delayed in appearance and diminished in intensity. Since the tips of all toes were fluorescent, we were sure that gangrene would not occur. The subsequent clinical course bore out our contention. In 2 cases the patient was seen so early that only severe pain and moderate cooling of the leg were present. There was no change in color except

19. Lesser, A.: Embolic Arterial Occlusion of Lower Extremities with Report of Four Successful Embolectomies and Review of Literature, J. A. M. A. **122**: 285-289 (May 29) 1943.

20. Bickel, W. H., and Ghormley, R. K.: Amputation Below the Knee in Occlusive Arterial Disease, Proc. Staff Meet., Mayo Clin. **18**:361-367, 1943.

for the faintest blanching without an ascertainable level. In these 2 cases a sharp level of fluorescein demarcation was demonstrated and there was no fluorescence below that level. In both cases the level was in the lower third of the thigh. After twenty-four and thirty-six hours, respectively, the massive bluish discoloration appeared and proved the accuracy of the prognosis. It indicated gangrene exactly at the level which marked the skin by means of the fluorescein test in combination with sympathetic block. In 7 cases comparative studies with cutaneous temperatures, oscillometry and palpatory observations were made, and in 2 tests with histamine wheals were carried out. Pulsations and oscillometric deflections had disappeared below the fluorescein demarcation line in all cases except 1. In this most puzzling case there were faint but distinct pulsations in the right femoral artery despite a bluish discoloration and coldness below Poupart's ligament. The fluorescein test showed a sharp line of demarcation around the thigh at the level of the groin. At a subsequent attempt at embolectomy it turned out that the pulsation was caused by a firm, well organized clot in the femoral and iliac arteries, which transmitted the pulsations from the aorta like a pencil. Generally the fall in cutaneous temperature was found in approximately the region where the fluorescein test indicated the vascular occlusion. It was, however, by no means as sharp as the fluorescein test. In 2 patients seen and tested within thirty minutes after the first sharp pain it appeared much later and long after the diagnosis of complete vascular occlusion was made with the fluorescein test.

Arterial and Arteriolar Thrombosis and Gangrene.—The decision is more difficult when an arterial thrombosis occurs in an arteriosclerotic leg. Here the staining of the tissue not affected by the occlusion may be poor owing to the generalized arteriosclerosis. Five cases were observed in which a long history of intermittent claudication and previous small areas of gangrene antedated sudden thrombotic occlusion of a larger vessel. In these cases there was no sharp line of demarcation and many fluorescent islands appeared in the otherwise nonfluorescent distal part. No hyperfluorescent area separated the normal from the gangrenous tissue. Apparently the preceding severe impairment of circulation had led to the establishment of many small but insufficient collaterals which did not permit the formation of a sharp line of demarcation at the time of the complete occlusion of the femoral artery. If there is doubt exactly where fluorescence ends, the Dermofluorometer provides a decision, for an increase in fluorescein skin units after the injection always indicates the presence of some circulation. This alone, however, does not determine whether this area should be included in the amputation. Only when the values are at least two thirds of the lowest normal, as shown in charts 4 and 5, may one safely refrain from amputation.

The decision to be made after sudden occlusion of a large artery is similar to that which can be made in cases of peripheral arteriosclerotic gangrene on the basis of the fluorescein test. We observed 72 cases in which small areas of peripheral arteriosclerotic gangrene appeared, in 43 instances as a complication of diabetes mellitus. Only the observations which have been impressive will be mentioned here. There seem to be two different types of peripheral gangrene. With one type, the one most frequently observed, there is a generalized marked decrease in fluorescence of both limbs with the appearance of an entirely nonfluorescent distal gangrenous area. Usually there is no hyperfluorescent ring surrounding the gangrenous tissue to indicate "walling off"; rather there is a definite trend toward further spread of the gangrene. The fluorescence of the entire limb is low. Dermofluorometer readings are more than one-third below the lowest normal (chart 6). In 87 per cent of the cases of this type which we observed the circulation time to the leg exceeded twice the arm-lip circulation time; sometimes it was six times as long. The ulcers showed no fluorescence of their base, which indicated complete ischemia. This type of condition offers an extremely poor prognosis, and an amputation must be performed at a high level. Low amputations lead to poorly healing stumps and necessitate further amputations, as we observed in 2 cases.

The second type of gangrene seems to occur subsequent to occlusion mainly of the smallest caliber arteries and the capillaries by local thrombosis. The fluorescein picture is considerably different. The ulcer may or may not show a few fluorescent capillaries. The surrounding tissue is extremely hyperfluorescent, with increased capillary permeability (positive reaction to spatula test). This hyperfluorescence may extend a few millimeters from the edge of the ulcer or sometimes several centimeters into the normal tissue. It indicates the vascular demarcation reaction of the surrounding tissue which usually seems to prevent further spread of the gangrene. The general fluorescence of the leg is normal or only slightly depressed. With these criteria 86 per cent of 27 patients had a normal arm to leg circulation time, while the remainder had only a slight elevation. This does not preclude the appearance of a gangrenous spot with the same

picture of good demarcation within a short time in another area. In our experience patients with this type of arteriosclerotic gangrene do well with local débridement and self demarcation. In 6 cases we could predict that gangrene would probably occur in a certain spot on the foot within a short time, for this area of the skin showed no, or a markedly diminished, fluorescence. In 3 of these there was no visible discoloration with ordinary light, while there was a reddening in the other 3. In all 6 gangrene occurred in the predicted area within two weeks or less.

Thromboangiitis Obliterans.—Because of the peculiar composition of our material we were able to study only 11 cases of thromboangiitis obliterans (Buerger's disease). In the fluorescein examination several features were outstanding. Seven patients showed a mottled fluorescence of their legs and feet, i. e., penny-sized areas of hypofluorescence interchanged with surrounding small areas of normal fluo-

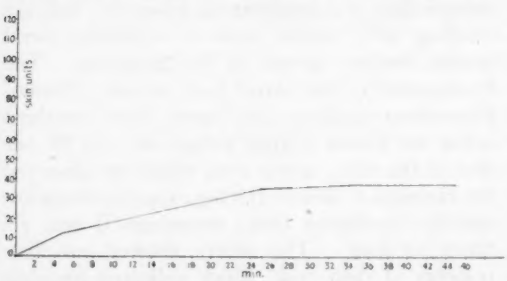

Chart 6.—Severe arteriosclerosis of the larger vessels of the leg with gangrene of the toes. Dermofluorometer curve of the leg.

rescence. The picture is similar to the marble skin seen under normal light, although marble skin was actually present in only 2 cases. In general, fluorescence of the legs was normal or slightly diminished, in decided contrast to the oscillometric values which were low or absent in all. This apparent discrepancy is explained by the fact that in thromboangiitis obliterans collateral circulation often takes excellent care of the basic requirements of the tissue. Gangrenous areas were well walled off by a hyperfluorescent margin. If a discrepancy between greatly reduced oscillometric values and good fluorescence is found in a younger person, the diagnosis of thromboangiitis obliterans is probably justified.

Vasospastic Disorders.—The opposite picture is observed in vasospastic disorders. Six young males complained of sudden attacks of severe coldness of the feet and part of the legs (and 1 also of the hands), usually occurring after excitement and lasting for a few minutes to several hours. Numbness and tingling accompanied these attacks. During, as well as apart from, the attacks, the peripheral pulses were palpable and the oscillometric values only very slightly decreased. The fluorescence of the feet and the temperature were greatly decreased. The appearance of the dye in the feet as measured with the Dermofluorometer was delayed, and the intensity was low. The symptoms were bilateral. With a procaine block of the second to the fourth lumbar sympathetic ganglion on one side, this side immediately assumed a much higher fluorescence than the opposite and its cutaneous temperature increased. The contrast was striking. Three patients were operated on, and bilateral sympathetic ganglionectomy resulted in complete cure for the period of observation, two years for 2 patients and eight years for the other. The "cured" patients have a fluorescence somewhat higher than normal and a rapid circulation time to the legs. Chart 7 depicts the fluorescein curve of one of the patients recorded with the Dermofluorometer before and after the ganglionectomy.

Since slight inflammatory changes are revealed clearly, patients with arteriosclerotic vascular disease may have strong fluorescence in a region where clinically the blood supply is apparently poor. An area of hyperfluorescence in a poorly fluorescent limb indicates that inflammatory reactions have started in an extremity meagerly supplied with blood. A positive reaction to the glass spatula test indicates increased capillary permeability due to the inflammation. Therefore, one is able to state clearly whether the reddish bluish discoloration of a foot, for example, is due to stasis (rubor on dependency) or to beginning gangrene on an infectious basis. In the former case the foot is *hypo*fluorescent; in the latter it is extremely *hyper*fluorescent. This differentiation is of importance for the immediate prognosis.

In 5 cases of arteriosclerotic vascular disease in which an inflammatory reaction of one foot could be discovered with the fluorescein test intense golden streaks extended up to the midcalf. There was no visible reddening of the skin in these areas. The fact that the course of the fluorescent streaks corresponded to the course of the superficial veins indicated that the inflammatory process extended upward along the veins. There was no hardening of the veins palpable.

Thrombophlebitis.—In 11 cases of acute superficial thrombophlebitis there was an exact outline of the inflammatory area marked by a golden streak on the skin. In 4 cases no cutaneous reddening was demonstrable under normal light.

In the remaining 7 cases extension of the hyperfluorescence several centimeters beyond the reddened skin indicated that the inflammation involved a larger area than the redness showed. Hyperfluorescence disappears soon which suggests that the inflammatory stage has subsided, but this happens much later than the red streak vanishes.

Varicose Vein Ulcers.—Sixty-six ulcers of the leg on the basis of varicose veins were studied. The characteristic of a varicose vein ulcer in the fluorescein test is poor fluorescence of its edges, especially where the ulcer has a tendency to extend. Usually the ulcer itself fluoresces poorly. Small islands of good fluorescence occur in a nonfluorescent or a very poorly fluorescent field. The appearance of the ulcer under normal light need not necessarily correspond to these manifestations. The normally fluorescent areas may look no brighter red than those of stasis, as indicated by a negative response to the fluorescein test. However, if Davis grafts are used therapeutically

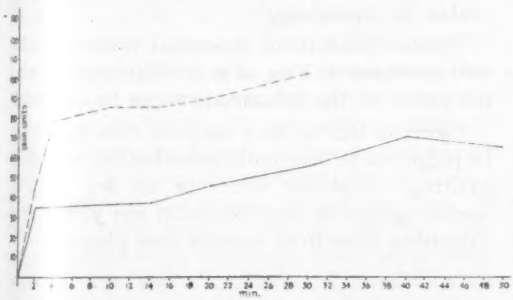

Chart 7.—Curves of a patient with a vasospastic disorder of the legs. The full line represents the Dermofluorometer curve of the left leg without blockage of the sympathetic ganglions; the broken line represents the Dermofluorometer curve of the right leg taken six days after ganglionectomy of the second to the fourth lumbar ganglion.

they should be implanted only on fluorescent spots, since they will not "take" in other areas. Since our experiences with skin grafts have been published elsewhere,[21] they will not be elaborated on here. Additional scraping until a fluorescent layer is reached is necessary for successful grafting in nonfluorescent areas. Sometimes the picture may be distorted when a layer of fibrin covers the surface of the ulcer. If this layer is removed capillaries which show fairly normal circulation are found. The test permits the observer usually to predict in what direction the ulcer is going to break down (nonfluorescence of certain parts of the margin). The general tendency of an ulcer of the leg to heal can be determined by the number of fluorescent islands in the ulcer. An ulcer of nonvascular origin with normal granulations and good healing tendency is highly fluorescent throughout. The effectiveness of mecholyl iontophoresis, for example, can be clearly judged by this test.

Syphilitic Ulcers.—Four syphilitic ulcers of the leg were observed. Usually the margin of such an ulcer is poorly fluorescent, especially in the direction where further breakdown is going to occur. The base of the ulcer is fully fluorescent, which shows that the capillaries of the granulations are well supplied with blood; the skin alone has the disturbance in the capillaries.

The test is valuable in establishing an immediate prognosis of frostbite. This subject will be reported on in a separate paper. The same fundamental principle is involved, and the subsequent occurrence of gangrene and the effectiveness of therapeutic measures can be predicted.

In general, the test seems to have distinct advantages over methods formerly employed, since it gives a direct insight into nutrition of the tissues in peripheral vascular diseases. It is necessary, however, for a complete survey of the functional capacity of the vessels of the limb to perform the usual tests, such as determinations of cutaneous temperature and oscillometric studies, in order to obtain as complete a picture as possible.

SUMMARY

Fluorescein when injected intravenously can be made visible by a beam of long wave ultraviolet radiation on reaching any area of exposed skin or mucous membranes with the blood stream.

The physical prerequisites for a good visualization of fluorescein in the tissue and capillaries are the use of an appropriate long wave ultraviolet ray source and a dark room. A photoelectric method to indicate the arrival of the dye and to measure the intensity of staining may also be used.

Fluorescein is not toxic. Over 1,000 patients have been examined by this method without untoward reactions, except that 11 patients had vomiting of short duration during the injection. Experiments on animals showed extremely low toxicity. The dye travels with the blood stream and diffuses immediately through the capillaries into the interstitial spaces. Dead cells do not stain. Fluorescein is partly adsorbed to the plasma proteins. Pathologic changes in plasma proteins do not change the amount of fluorescein immediately available for diffusion.

21. Lange, K.: The Vascular Prerequisites of Successful Skin Grafting, Surgery **15**:85-89, 1944.

Ultrafiltration experiments show that the amount of dye diffusing into the tissue depends on intracapillary pressure; if the latter rises the amount which diffuses into the tissue with the water increases without changing the concentration. Changes in capillary permeability change the amount which diffuses as well as the concentration. Even slight inflammation increases the fluorescence of the tissue. Pigmentation, especially in colored people, makes the test unreliable, although certain basic facts can still be elicited. The degree of fluorescence depends on the amount of blood flowing through a certain part of the body. Objective determinations of circulation time in normal persons showed that the circulation time between the arm and the lips is between fifteen and seventeen and a half seconds, while the time to the legs normally should not exceed twice this figure.

Nine patients with acute embolism of the legs were examined. It was possible to define exactly the lowest possible level of amputation as far as the skin is concerned and to decide immediately on the probable formation of sufficient collateral circulation to avoid amputation.

Block of the sympathetic lumbar ganglions should be performed to avoid mistakes caused by vasospasm.

The immediate diagnosis of thrombotic occlusion can also be made.

Small gangrenous areas in arteriosclerotic peripheral vascular disease can be judged as to the prospect for healing, localization or further spread.

There are two functional types of arteriosclerotic peripheral vascular disease as shown by this test. The first form concerns the larger vessels, mainly causing rapidly spreading gangrene in the periphery, while the other occludes mainly small arteries with capillaries, thereby not necessitating large amputations.

Thromboangiitis obliterans has usually a higher fluorescence than one would expect from the lack of arterial pulsations. This discrepancy is a leading sign. Spotty fluorescence may complete the picture.

Vasospastic disorders have a low fluorescence during the attack, which immediately reutrns to normal or even increases above normal on blockage of the sympathetic chain.

Rubor on an inflammatory basis in a limb with arteriosclerotic peripheral vascular disease can be well differentiated from venous congestion (rubor on dependency).

Thrombophlebitis of superficial vessels can be well made out as long as it is inflammatory and the extent of the inflammation can be outlined.

Ulcers of the leg on a varicose vein basis can be judged as to their outlook for healing and skin grafting. Syphilitic ulcers of the leg have a specific picture in the fluorescein test which distinguishes them from varicose vein ulcers.

HEMATOLOGIC AND GENETIC STUDY OF THE TRANSMISSION OF THALASSEMIA

(COOLEY'S ANEMIA; MEDITERRANEAN ANEMIA)

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Cooley's anemia,[1] or thalassemia,[2] is a rare but well known disease. This fatal disorder is characterized by a chronic, progressive, hypochromic and microcytic type of anemia, peripheral erythroblastosis, increased number of target and oval red blood cells, decreased fragility of erythrocytes, splenomegaly, deposition of pigment in the viscera and changes in the bones. The condition was early noted to have a familial incidence and to be virtually restricted to the Mediterranean peoples. In 1937, Angelini (quoted from Wintrobe and associates[3]) observed that in some instances the erythrocytes of apparently healthy parents and of siblings of patients suffering from this anemia showed decreased fragility. Caminopetros[4] independently confirmed this observation, finding that 22 of 30 parents tested showed reduced fragility. He also reported slight changes in the bones in some parents. A few years later, Wintrobe, Matthews, Pollack and Dobyns[3] described the occurrence in several Italian families of a relatively mild anemia which did not respond to iron therapy. It resembled thalassemia in many respects but was quantitatively much less extreme. Erythrocytes were characteristically hypochromic and microcytic; ovalocytes and target cells were present, but no peripheral erythroblastosis was observed. There was a tendency toward splenomegaly and hyperplasia of the bone marrow. Fragility of the erythrocytes in hypotonic solution of sodium chloride was reduced. Shortly thereafter, Dameshek[5] and Strauss, Daland and Fox[6] described an apparently identical condition under the names of "target cell anemia" and "familial microcytic anemia." The final link relating this condition to thalassemia was provided by Wintrobe,[7] who confirmed Angelini's and Caminopetros' observation on the decreased fragility of the erythrocytes in the parents of persons having thalassemia. He further showed that the blood picture was abnormal in these parents, being identical with that of the mild anemia described previously. This observation was confirmed by Dameshek[8] and Smith,[9] who, in addition, found the same changes in the blood of some of the siblings of patients with thalassemia.

The purposes of the present paper are: (1) to present hematologic data on the parents, the siblings and some immediate collaterals of 3 persons who had thalassemia and of 1 person with the similar, milder condition; (2) to consider in some detail the hereditary aspects of this disorder, and (3) to emphasize the problem of the differential diagnosis and the clinical significance of the mild anemia.

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Drs. John S. Lawrence, William L. Bradford, G. H. Whipple, Curt Stern and Lawrence Young gave many helpful suggestions and valuable criticisms. Mrs. Priscilla Neel assisted in the preparation of figures.

1. Cooley, T. B., and Lee, P.: Series of Cases of Splenomegaly in Children with Anemia and Peculiar Bone Changes, Tr. Am. Pediat. Soc. **37**:29-30, 1925.

2. Whipple, G. H., and Bradford, W. L.: Mediterranean Disease—Thalassemia (Erythroblastic Anemia of Cooley), J. Pediat. **9**:279-311 (Sept.) 1936.

3. Wintrobe, M. M.; Matthews, E.; Pollack, R., and Dobyns, B. M.: A Familial Hemopoietic Disorder in Italian Adolescents and Adults, J. A. M. A. **114**:1530-1538 (April 20) 1940.

4. Caminopetros, J.: Recherches sur l'anémie erythroblastique infantile, des peuples de la Méditerranée orientale, Ann. de méd. **43**:27-61 (Jan.); 104-125 (Feb.) 1938.

5. Dameshek, W.: "Target Cell" Anemia: An erythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445-454 (Oct.) 1940.

6. Strauss, M. B.; Daland, G. A., and Fox, H. J.: Familial Microcytic Anemia, Am. J. M. Sc. **201**:30-34 (Jan.) 1941.

7. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

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9. Smith, C. H.: Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia, Am. J. Dis. Child. **65**:681-701 (May) 1943.

METHODS

The results of the present study, which embraces 34 patients, are recorded in tabular form by families. All hemoglobin readings represent the average of two or more determinations with carefully calibrated hemoglobinometers of the Sahli type. All erythrocyte counts represent the average of two or more counts from different pipets, made with counting chambers certified by the United States Bureau of Standards. The volume of packed red blood cells was determined by centrifuging in a Wintrobe hematocrit tube at a speed of 3,000 revolutions per minute for one hour. Samples were drawn collected in a similar manner. Studies were made in every case on venous blood, drawn without stasis into a dry, clean syringe. Blood smears and reticulocyte counts were made with capillary blood obtained from the lobe of the ear, except in 1 instance in which it was necessary to use venous blood, collected as described previously.

White blood cell counts and icteric index readings were determined for all persons studied. For only 3 persons did the leukocyte count exceed 10,000, and for none was it above 12,000. In our series no icteric index above 10 was noted. In the interests of conserving space, we have omitted detailed data on these two points.

TABLE 1.—*Summary of Blood Findings in Family Y. and Collaterals*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micro-micrograms	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Complete
C. Y., patient with thalassemia	6	5.40	2.36	19.2	5.4	81.4	22.9	28.1	4+	4+	3+	0.76 0.50*	0.20† 0.34
A. Y., mother	26	10.35	5.10	35.0	2.0	68.6	20.3	29.6	3+	2+	4+	0.46 0.50*	0.20† 0.32
S. Y., father	28	11.45	5.26	37.8	2.9	71.8	21.8	30.3	4+	1+	3+	0.50 0.50*	0.20† 0.32
S. Y. Jr., brother	4	10.80	5.87	34.2	1.4	58.2	18.4	31.6	3+	2+	1+	0.48 0.50*	0.20 0.34
C. Y., sister	2	9.40	5.23	32.0	1.2	61.2	18.0	29.4	4+	3+	4+	0.46 0.50*	0.20† 0.34
R. Y., aunt (P)‡	23	12.25	3.94	37.5	0.8	95.0	31.1	32.6	0	0	0	0.50 0.46*	0.26 0.30
G. L., aunt (P)	32	8.80	5.46	30.3	3.2	55.5	16.1	29.0	4+	2+	3+	0.46 0.50*	0.22 0.32
J. Y., uncle (P)	30	13.00	5.62	39.2	0.6	69.7	23.1	33.2	2+	1+	1+	0.44 0.50*	0.22 0.32
F. Y., uncle (P)	25	13.50	6.22	42.0	2.6	67.5	21.7	32.1	4+	2+	1+	0.44 0.48*	0.20† 0.30
C. Y., G-father (P)	67	14.25	4.75	44.8	1.4	94.2	30.0	31.8	0	0	0	0.46 0.50*	0.28 0.32
C. Y., G-mother (P)	63	12.80	5.42	39.0	1.2	72.0	23.6	32.8	4+	1+	3+	0.46 0.46*	0.22 0.30
G. M., aunt (M)§	18	11.90	6.27	38.8	2.4	61.9	19.0	30.7	3+	3+	2+	0.46 0.46*	0.22 0.30
J. M., aunt (M)	30	10.50	5.12	35.0	0.8	68.4	20.5	30.0	3+	2+	3+	0.42 0.46*	0.20† 0.30
M. M., uncle (M)	16	10.20	4.93	34.5	1.2	70.0	20.7	29.6	3+	3+	0	0.46 0.46*	0.20† 0.30
M. M., aunt (M)	10	11.30	5.40	36.2	0.8	67.0	20.9	31.2	3+	3+	2+	0.44 0.50*	0.30 0.32
D. M., aunt (M)	32	14.00	4.56	40.5	2.2	88.6	30.7	34.6	0	0	0	0.48 0.50*	0.30 0.32
P. M., uncle (M)	19	16.10	4.93	47.0	0.2	95.4	32.6	34.2	0	0	0	0.50 0.52*	0.32 0.34
J. M., uncle (M)	25	15.00	4.69	42.8	0.8	91.2	32.0	35.1	0	1+	0	0.48 0.52*	0.30 0.34
F. M., G-father (M)	57	12.40	6.05	39.8	1.6	65.8	20.5	31.2	2+	2+	1+	0.46 0.50*	0.20 0.32
C. M., G-mother (M)	55	12.80	4.35	39.5	1.6	90.9	29.4	32.4	0	0	0	0.50 0.50*	0.30 0.32

* Control determination.
† Incomplete hemolysis at 0.20.
‡ (P) paternal.
§ (M) maternal.

from blood in which the anticoagulants potassium and ammonium oxalate were present in such proportions that there was no alteration in the volume of erythrocytes.[10] All blood was thoroughly mixed before each sample was withdrawn. Samples used in determining the fragility of the erythrocytes in hypotonic solutions of sodium chloride were obtained from the same source and controlled in every instance by concomitant testing of the blood of young and healthy members of the hospital staff,

In the pedigrees presented with each family, we have indicated our interpretation of the hematologic data, i. e., whether a subject was normal, was mildly affected or revealed clinical thalassemia. It should be emphasized now that in some persons designated as showing the mild anemia the changes were very slight, although in only 1 or 2 instances was there any doubt as to whether a person was normal or abnormal.

PRESENTATIONS OF DATA

FAMILY Y AND COLLATERALS: (Fig. 1 and Table 1).—The study of this large and cooperative Italian family was undertaken because one of its members, C. Y., a girl

10. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777-780 (April) 1934.

6 years of age, had been followed in the pediatric clinic for thalassemia since she was 4 months old. The patient was born in the Strong Memorial Hospital and followed in the well baby clinic without evidence of the disease until the age of 3 months, when pallor was observed and ferrous sulfate prescribed. At the age of 4 months, the pallor was more evident. The skin showed

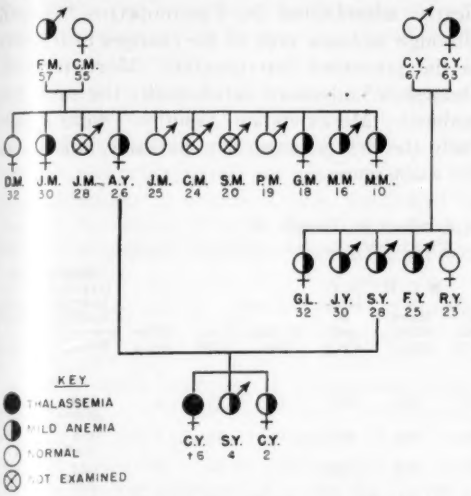

Fig. 1.—Pedigree of Family Y and collaterals.

a slight yellow-brown color. The liver was slightly enlarged, and the spleen was palpated 4 cm. below the left costal margin. The patient was admitted to the hospital, where she was found to have the typical blood picture

remaining 3 were in the armed services and not available) and all the maternal and paternal grandparents. To the best of their knowledge, none of the members studied had existing disease. Shortly after the completion of our studies, on Aug. 17, 1943, the patient died of a fulminating septicemia.

Family Sc. (Fig. 2 *a* and Table 2).—This family, of Sicilian extraction, was made up of the siblings and the parents of J. Sc., who was reported on as a patient with thalassemia by Whipple and Bradford[2] (case 3), with full clinical history and observations at autopsy. No members of this family were aware of existing disease.

Family Si. (Fig. 2 *b* and Table 3).—This Sicilian family was composed of the siblings and the mother of E. S., whose case has been reported with full details as an instance of thalassemia by Whipple and Bradford[2] (case 8). The patient died in Strong Memorial Hospital on March 13, 1940. The father of the family had died of rheumatic heart disease. All members studied considered themselves in robust health.

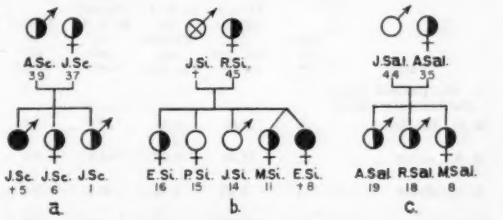

Fig. 2.—*a*, pedigree of Family Sc.; *b*, pedigree of Family Si.; *c*, pedigree of Family Sal.

Family Sal. (Fig. 2 *c* and Table 4).—Our attention was attracted to this Italian family not because of the presence of a known case of thalassemia but because of

Table 2.—*Summary of Blood Findings in Family Sc.*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micromicrograms	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Complete
J. Sc., patient with thalassemia (dead)													
J. Sc., mother.....	37	14.30	5.23	42.0	0.6	80.3	27.4	34.0	1+	3+	0	0.46 0.48*	0.28 0.32
A. Sc., father.....	39	15.20	6.27	46.4	0.8	73.9	24.2	32.8	2+	1+	1+	0.46 0.48*	0.26 0.32
Joan Sc., sister.....	6	13.25	5.33	39.0	0.3	73.0	24.8	34.0	1+	1+	0	0.42 0.48*	0.28 0.32
John Sc., brother....	1	11.60	5.16	40.7	0.6	78.9	22.4	28.5	2+	2+	0	0.42 0.48*	0.26 0.32

* Control determination.

of thalassemia, with a large number of nucleated erythrocytes in the peripheral blood. Roentgenographic evidence of bone changes compatible with early thalassemia was obtained at this time. Splenectomy was performed at the age of 6 months to rid the child of a cumbersome organ, which was producing digestive disturbances by pressure. Subsequent to that time the patient had thirty-one admissions—most of them for infections of the respiratory tract or transfusions. Each time the characteristic erythroblastic anemia was present. Changes in the bones, as observed in roentgenograms, became more prominent, but mongoloid facies was never a particularly outstanding feature. We were fortunately able to study all the patient's siblings (2), the mother and the father, all the living paternal aunts and uncles (4), 7 of 10 living maternal aunts and uncles (the

a peculiar blood picture in one of the children, R. Sal., admitted to the medical service with a three day history of nausea, vomiting and fever. The symptoms quickly subsided but were never adequately explained. However, the patient consistently showed a markedly elevated erythrocyte count without proportional increase in the hemoglobin and the volume of packed erythrocytes. The blood smear showed hypochromic erythrocytes, microcytes, target cells and oval cells. The erythrocytes were abnormally resistant to hypotonic solution of sodium chloride.

This patient had been followed since 1939 with a diagnosis of probable rheumatic fever. The diagnosis rested on (1) recurrent attacks of abdominal pain, nausea, vomiting and fever without demonstrable cause and unassociated with a migratory polyarthralgia, (2)

systolic mitral murmur, (3) slight tendency toward a right axis deviation shown by electrocardiogram, (4) slight prominence of the pulmonary conus, shown by roentgenograms and (5) history of decreased tolerance for exercise. Perusal of the patient's record revealed that in each of these episodes the sedimentation rate was low normal. In retrospect, the diagnosis appears open to question. Dameshek [8] emphasized that an erroneous diagnosis of rheumatic fever may be made for persons presenting the hematologic picture shown by this patient. The mother, the father and 2 siblings of this patient were studied.

THE GENETICS OF THALASSEMIA

The foregoing data are similar in all essential respects to those on the cases reported by Wintrobe and co-workers,[5] Wintrobe,[7] Dameshek,[11] Strauss, Daland and Fox [6] and Smith.[9] The existence of a mild familial anemia qualitatively similar to thalassemia and the presence of this anemia in both the parents and many of the siblings of patients having thalassemia must be regarded as well established facts. However, the exact genetic relationship of these two blood dyscrasias has remained unclear. Three chief theories have been advanced.

1. Thalassemia is owing to homozygosity for a factor which when heterozygous produces the mild anemia; i. e., the factor responsible for thalassemia is either an incomplete recessive or a semidominant. Otherwise stated, full-blown thalassemia is inherited as a recessive characteristic, but the heterozygote as well shows significant changes in the blood. This theory was clearly adumbrated in Caminopetros' [4] paper, although he knew only of the changes in fragility in the presumed heterozygote. More recently, Dameshek [8] advanced substantially the same hypothesis. Moncrieff and Whitby [12] were apparently the first to suggest a recessive inheritance for thalassemia.

TABLE 3.—*Summary of Blood Findings in Family Si.*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micro-micro-grams	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Complete
E. Si., patient with thalassemia (dead)													
R. Si., mother	45	11.65	5.86	38.0	3.6	64.7	19.9	30.6	1+	1+	0	0.50	0.24
												0.50*	0.32
M. Si., sister	11	12.90	6.30	42.8	0.8	68.0	20.5	30.2	1+	1+	2+	0.46	0.28
												0.50*	0.32
P. Si., sister	15	14.10	5.08	40.8	0.6	80.3	27.8	34.6	0	0	0	0.52	0.32
												0.50*	0.32
J. Si., brother	14	15.75	5.08	44.2	0.4	87.0	31.0	35.6	1+	0	0	0.46	0.30
												0.50*	0.32
B. Si., sister	16	10.50	4.98	35.0	0.4	70.2	21.1	30.0	0	1+	1+	0.48	0.30
												0.50*	0.32

* Control determination.

TABLE 4.—*Summary of Blood Findings in Family Sal.*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micro-micro-grams	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Complete
R. Sal., patient	18	12.80	6.61	44.0	1.6	66.5	19.3	29.1	2+	2+	1+	0.44	0.22
												0.50*	0.34
A. Sal., mother	35	12.00	5.73	40.0	0.8	69.9	20.9	30.0	1+	2+	0	0.42	0.22
												0.48*	0.28
J. Sal., father	44	15.40	5.35	46.5	0.6	87.0	28.8	33.1	0	0	0	0.44	0.28
												0.48*	0.32
Anthony Sal., brother	19	14.15	6.60	48.0	0.4	72.8	21.4	29.5	2+	2+	1+	0.42	0.30
												0.46*	0.32
M. Sal., sister	8	11.15	5.57	35.5	0.6	63.7	20.0	31.4	2+	3+	0	0.42	0.22
												0.48*	0.38

* Control determination.

2. Cooley [13] and Smith [9] suggested that the severe and the mild condition have the same genetic basis and are due to a dominant factor which is variably expressed. In one person heterozygous for this factor an extreme degree of thalassemia may develop, whereas in another heterozygote there may be only slight changes. Presumably the different reactions of these two persons are determined by environmental and genetic modifiers.

11. Dameshek (footnotes 5 and 8).

12. Moncrieff, A., and Whitby, L. E. H.: Cooley's Anemia, Lancet **2**:648-649 (Sept. 22) 1934.

13. Cooley, T. B.: Hereditary Factors in the Blood Dyscrasias, Am. J. Dis. Child. **62**:1-8 (July) 1941.

3. Finally, McIntosh and Wood [14] proposed that thalassemia is caused by the simultaneous presence of two nonallelomorphic dominant factors, one inherited from each parent.

It is apparent that these three theories differ widely in the genetic mechanism which they postulate. The following considerations are pertinent in reaching a decision as to which of these is most probable.

1. In every case in which *complete* hematologic studies have been carried out on the parents of patients having thalassemia, *both* parents have shown some significant abnormality. The only exception to this is a case mentioned by Smith,[9] the details of which have not been published. If a single, variably expressed dominant factor were responsible for the disease, in the great majority of the families only one parent would be expected to show an abnormal blood picture. In order to produce thalassemic offspring, it would be enough that 1 per cent should show changes, and since marriages between two affected people would be much rarer than between a normal and an affected person, most persons having thalassemia would be the issue of the latter type of marriage. If the condition is due to the interaction of two dominant factors, as suggested by McIntosh and Wood, one is required to make the improbable assumption that each of these has the same phenotypic effect, since otherwise there would be no reason for both parents to show similar hematologic changes. If, however, as postulated in theory 1, the mild condition is due to the heterozygous state for the "thalassemia factor," both parents would be expected to show changes, since only from a marriage of two such heterozygotes would a homozygous thalassemic offspring result. In view of the great variabilty in the expression of the mild condition, it is not impossible that rarely a heterozygote may overlap with a normal person and not be detectable by present hematologic methods. The case mentioned by Smith [9] might be such an instance. Mrs. A. Sc. and Joan Sc. in our series (table 2) show only very slight, albeit significant, changes.

2. The proportion of nonthalassemic to thalassemic children in segregating families supplies certain clues as to the genetic mechanism involved. While a given ratio can rarely be used as proof of a hypothesis, it may render one possibility more likely than another. According to the first and third theories just described, an approximation to a 3:1 ratio should be observed, when allowance is made for distorting factors. The approximate ratio to be expected from theory 2 cannot be estimated, since the penetrance of the postulated variable dominant factor is unknown. Table 5 summarizes the available data on this point. It is unfortunate that many of the case reports in the

TABLE 5.—*A Compilation of Families Yielding Cases of Thalassemia and an Analysis of the Observed Proportions for Agreement With a Three to One Ratio*

Size of Family	Number of Such Families	Thalassemic Members: Observed	Thalassemic Members: Expected on 3:1 Basis	$\eta_3\sigma_{\eta_3}{}^2$
1	8	8	8.0000	0.00000
2	9	11	10.2852	1.10205
3	22	32	28.5406	5.78534
4	8	15	11.7024	3.36040
5	9	14	14.7501	5.32609
6	3	5	5.4744	2.32785
7	3	5	6.0588	2.91072
8	..	..	.....	.....
9	1	2	2.4328	1.3802
10	..	..	.....	.....
11	1	3	2.8710	1.8053
	64 (228 children)	95	90.1153	23.99788

* $\sigma = \sqrt{23.99788} = 4.9$

literature do not list the total number of thalassemic and nonthalassemic children in a given family but state merely that "one sibling was likewise affected," or "the remaining children were normal." In the 64 families for which a complete record was available, 133 nonthalassemic and 95 affected children were present—a ratio of 1.4:1. On the surface, this is a significant departure from 3:1. However, numerous investigators have noted that genetic ratios are grossly distorted in small human families by the fact that all families from heterozygous parents in which no affected child happens to be present remain undetected, i. e., only families with at least 1 affected child are studied. Numerous methods for making allowance for this error have been proposed. When these data are analyzed by Hogben's [15] method for compliance with a 3:1 ratio, excellent agreement is observed, the departure from expectation being approximately one times the error of expectation. No other simple genetic ratio so nearly fits the data. While a variably expressed dominant factor might, by chance, give such a ratio, the assumption of a recessive inheritance for full-blown thalassemia is more likely. McIntosh and Wood [14] likewise noted an agreement with a 3:1 ratio but discarded the hypothesis of a recessive factor because they felt that the incidence of consanguineous marriage among the parents was not as high as would be expected when so rare a factor was involved. Actually, however, we have no reliable estimates of the

14. McIntosh, R., and Wood, C. L.: An Inquiry into the Genetic Factor in Cooley's Anemia, Am. J. Dis. Child. **64**:192-193 (July) 1942.

15. Hogben, L.: Nature and Nurture, New York, W. W. Norton & Company, Inc., 1933.

frequency of the disease among the Sicilians and the Greeks, the peoples in whom it most commonly occurs. It is probably more frequent than thought. Furthermore, many of the data have been collected without attention to the determination of consanguinity, so that we are in no position to estimate the importance of this factor.

3. The ratio of normal to affected children in marriages between a normal person and one showing slight changes is also of interest. Only a few marriages have been completely analyzed from this standpoint. If thalassemia is due to a variable dominant factor, some of the children of such a marriage should show the disease. The significance of the fact that this has not been reported has already been mentioned. If the mild state is due to heterozygosity for the thalassemia factor, an approximation to a ratio of 1 normal person to 1 mildly diseased person would be expected among the children of such marriages. A similar ratio would be expected if the disease is due to the simultaneous presence of two dominant factors, which when acting separately induce mild changes. The results of such marriages are summarized in table 6. The criteria for the inclusion of families in this table

TABLE 6.—*The Segregation Into Normal and Mildly Anemic Children of Marriages Between Normal and Mildly Anemic Persons and an Analysis of the Results for Agreement With a One to One Ratio*

Number of Children Examined from Family	Number of Such Families	Anemic Members		
		Observed	Expected on 1:1 Basis	$\eta_s\sigma_s$*
1	2	2	2.000	0.0000
2	4	7	5.332	0.8888
3	3	8	5.145	1.4694
4	1	3	2.134	0.7822
5	1	4	2.581	1.082
6	..	..	.....	.....
7	..	..	.....	.....
8	2	12	8.030	3.890
	13 (44 children)	36	25.222	8.1124

* $\sigma = \sqrt{8.1124} = 2.85$

have been: (1) Both parents must have been examined and one definitely found normal and the other abnormal, and (2) hematologic data must have been published in support of these conclusions. These criteria are necessary to exclude cases in which only one parent was studied and the other (unstudied) might also have had mild anemia—but by chance no thalassemic children were born of the mating. On this basis, all of the data of Strauss, Daland and Fox [6] and of Dameshek [5] have been omitted from the table. The observed ratio is 4.5:1.0 (data of Wintrobe and co-workers,[3] Dameshek [8] and Smith [9] and our own in this paper). Even when allowance is made for the distortion of sampling errors, there is a significant excess of the mildly affected persons on the basis of a 1:1 ratio, the difference between observation and expectation amounting to three and eight-tenths times the standard error of the difference. The departure from a 1:1 ratio appears to exist whether the factor is carried by the male or female parent, although the numbers involved are admittedly small. Thus, when the father was the carrier, the ratio of carrier to normal was 11 : 4, while with the mother the carrier, the ratio was 25:4. The results of such marriages, therefore, do not conform to expectation on the basis of any of the three hypotheses outlined here.

4. In a few marriages (data of Wintrobe and co-workers,[3] Dameshek [8] and Smith [9] and our own in this paper) in which both parents are known to have shown the slight changes of the mild anemia or in which the marriages have come to attention because of the birth of a child having thalassemia and hence the parents may safely be assumed to have had slight changes, the segregation of the offspring into normal, mildly affected and thalassemic children has been studied. If thalassemia is due to an incomplete rceessive factor, then among the nonthalassemic offspring of such a marriage, a ratio of 2 mildly affected to 1 normal child is expected, and this ratio is not subject to any distorting factor. If the disease is due to a variable dominant factor, then the ratio would be something less than 2:1, since many of the heterozygotes would be phenotypically indistinguishable from the homozygotes. Finally, a 2:1 ratio would also be expected when two independently inherited dominant genes were involved. Actually, the ratio observed in a total of 13 families is 15 thalassemic patients to 17 persons showing only slight changes to 8 normal persons. While the numbers are entirely too small to permit any certain conclusions, it is interesting to note that the ratio of mildly affected to normal persons is so nearly 2:1.

5. Wintrobe, Matthews, Pollock and Dobyns,[3] Wintrobe [7] and Dameshek [8] emphasized the existence of a continuous series of conditions grading from mild changes to severe thalassemia. There is little doubt that one can select cases to form such a series. However, what is more germane to the present consideration is the distribution of types within this series of cases. If the entire gamut is due to a variable dominant factor, one might reasonably expect a unimodal distribution of the percentages of the various types, but if two different genetic conditions, a homozygous and a heterozygous, are involved, a bimodal distribution is the more prob-

able. While exact data on this point are difficult to collect, it is our impression that the blood pictures fall into two fairly well defined groups, one mild (nonthalassemic) and the other severe (thalassemic), with only a relatively few cases of intergrading.

We may now summarize the bearing of these considerations on the validity of the theories which have been proposed. The observations of sections 1, 2, 4 and 5 are compatible with the first hypothesis, that of an incomplete recessive character. The observations of 2, 4 and 5 are also compatible with the third hypothesis. The decision between these two rests, at present, squarely on the inherent improbability of encountering a condition such as this due to two independent factors, in which each of the factors involved has an identical phenotypic effect. It might be possible to differentiate between the two theories on the basis of a statistical evaluation of a large number of marriages in which the segregation into the three types had been studied, but such a series would have to be many times as extensive as that presented here. Hypothesis 2, of a variable dominant factor, fails to account for the bulk of the facts.

It should be stressed that none of the theories explains the results summarized in section 3. There appears to be a significant excess of the mildly anemic type among the offspring of mildly anemic and normal parents. This excess is apparent in all the investigations thus far reported. Misclassification as a cause seems unlikely. Should further work bear out this tendency, it will be necessary either to seek a distorting factor or to evolve a new theory more consistent with all the data. In this connection, we have considered several alternate, more complex possibilities and have found that none of them comes closer to satisfying all the facts. For the present, it seems best to view the hypothesis of an incomplete recessive character as the most satisfactory working approach to the problem, pending the collection of further data.

DETECTION OF CARRIERS OF THALASSEMIA

Regardless of the ultimate genetic mechanism involved in the transmission of thalassemia, the fact remains that there are certain persons who may be designated as carriers of the disease. If the carrier state is to be diagnosed with any accuracy and assurance, it is obvious that the criteria for the diagnosis must be clearly promulgated. It is equally obvious that, owing to relatively wide variations in the severity of the carrier state, these criteria cannot be completely rigid. Dameshek [8] pointed out that the diagnosis rests on a racial factor, a hypochromic condition of the blood refractory to iron therapy, the presence of target, oval and stippled cells in the blood smear, an increased resistance of erythrocytes to hypotonic solutions of sodium chloride and the absence of other conditions in which target cells are found. Amplification and further discussion of certain of these criteria would seem desirable.

The hypochromic and microcytic blood picture is best illustrated and expressed by the constants mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. In our experience, the mean corpuscular volume and the mean corpuscular hemoglobin were frequently much lower than those in any but the most severe iron deficiency anemias. The mean corpuscular hemoglobin concentration, on the other hand, was often lowered to a much less remarkable degree. This is in accordance with the view that the defective cell is thin and has a volume considerably below normal but for its volume is only moderately deficient in hemoglobin. Whether the absolute value of hemoglobin in grams per hundred cubic centimeters of blood is normal or below normal and whether the erythrocyte count is diminished, elevated or within normal limits are of consequence chiefly in that they reflect differences in individual ability to compensate for the abnormalities present. It is the relationship between the hemoglobin content, the erythrocyte count and the volume of packed red cells that is of diagnostic significance. That these relationships in some instances may not be so dramatically abnormal must be admitted.

The presence of frequent target and oval cells on blood smears led Dameshek [8] to refer to the carrier state as a "target-oval cell syndrome." What has not been adequately pointed out is the fact that in persons showing evidence of the carrier state the blood smear may vary from one in which target cells are abundant to one in which there are excessive numbers of oval cells with rare target cells. Figure 3 serves to illustrate such variations. Hypochromia of erythrocytes on smears has in our experience been slight to moderate, correlating rather closely with the slightly to moderately lowered mean corpuscular hemoglobin concentration. That the erythrocytes are small can also be readily proved by Price-Jones cell measurements. Figure 4 shows the result of such a study made on family Sal. Basophilia and reticulocytosis apparently vary considerably in different persons

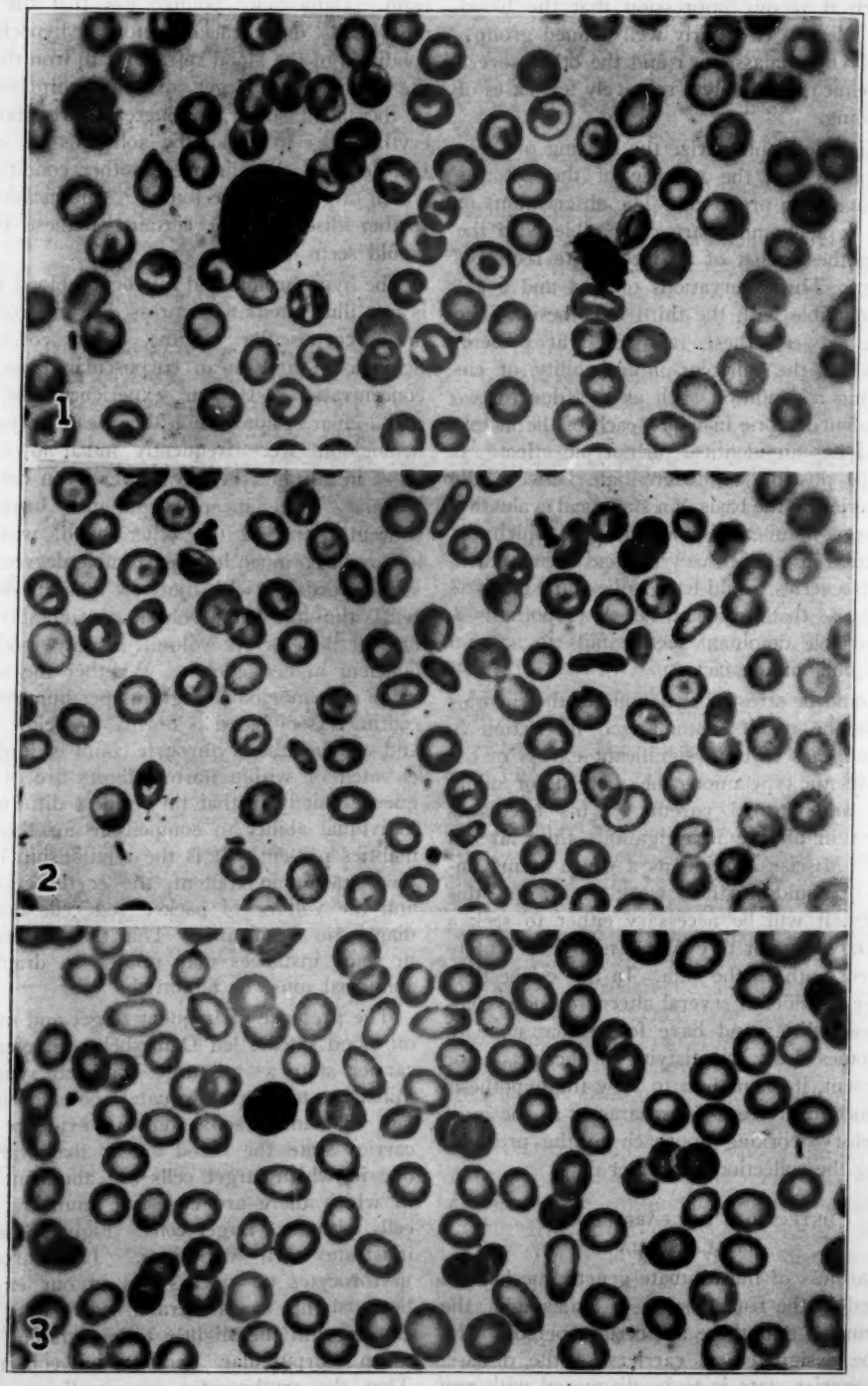

Fig. 3.—Photomicrographs (oil immersion; × 970) showing differences in the blood smears of carriers: *1*, blood smear of F. Y. (table 1), showing numerous target cells; *2*, blood smear of M. M. (10) (table 1), showing numerous target and oval cells; *3*, blood smear of J. Sc. (37) (table 2), showing mild ovalocytosis.

Bradford and Dye [16] were the first who proposed that erythrocytes in thalassemic persons are abnormally thin. Wintrobe and co-workers [3] and Dameshek [5] postulated that thin erythrocytes

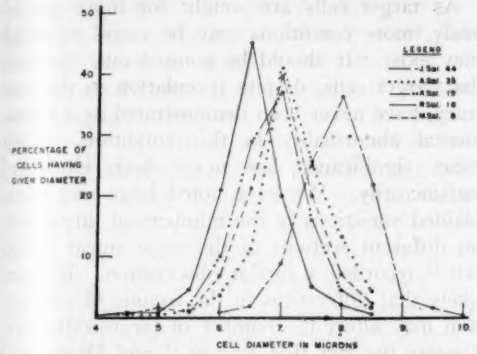

Fig. 4.—Distribution of erythrocytes according to size (Price-Jones curves) in the blood of members of an Italian family (Sal.), based on measurements of 400 cells for each member.

in the carrier are responsible for the increased resistance of erythrocytes to hypotonic solutions of sodium chloride. Barrett's [17] studies indicated that the target cell is a thin, resistant cell. The fact that increased resistance usually exists is further confirmed by our data, although the fragility of erythrocytes is not significantly altered in certain persons with ovalocytosis and only mild abnormalities. Yet the weight of evidence indicates that such persons are carriers.

Predominant ovalocytosis in Mrs. Sc. (table 2), which constituted the chief evidence of the existence of the carrier state, deserves some further comment. Stephens and Tatelbaum [18] reported from this laboratory in detail the hematologic findings for an Italian patient having ovalocytosis. About half the immediate family and other close relatives of the patient likewise showed an ovalocytic blood picture. In such persons the consistently lowered mean corpuscular volumes and mean corpuscular hemoglobin, the moderately lowered mean corpuscular hemoglobin concentrations and the tendency toward an elevated erythrocyte count were analogous to our observations on the carriers of thalassemia. It was decided, therefore, to reinvestigate R. I. and her 2 affected offspring. This was done with confirmation of the data obtained in 1934 (table 7). In addition the erythrocytes were found to have slightly increased resistance to hypotonic solutions of sodium chloride, rare target cells were found in every instance and basophilic stippling was frequently noted. The changes in fragility of the erythrocytes were not dramatic. The close analogies present suggested that the condition in this family, as well as some other reported instances of familial ovalocytosis in Mediterranean peoples, represented the carrier state of thalassemia.

TABLE 7.—*Summary of Blood Findings in Family I.*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micro-micro-grams	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Complete
R. I., mother.....	44	11.50	5.33	38.3	1.6	71.9	21.6	30.0	1+	4+	4+	0.44	0.26
												0.48*	0.32
J. I., daughter.....	17	10.90	5.05	37.0	2.6	73.3	21.6	29.4	2+	3+	3+	0.44	0.26
												0.48*	0.32
S. I., son.....	19	12.80	5.71	44.0	1.0	77.0	22.4	29.1	1+	4+	3+	0.44	0.24
												0.48*	0.32

* Control determination.

Little has been reported concerning decreased fragility of erythrocytes in person with thalassemia itself. Figure 5 illustrates that increased resistance of erythrocytes to hypotonic solutions of sodium chloride may at times be very marked.

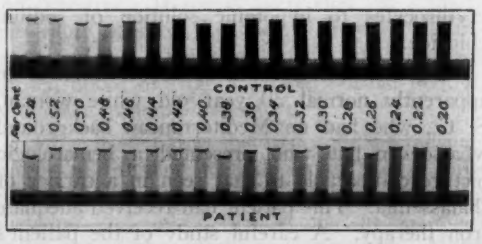

Fig. 5.—Photograph of results of fragility test on the blood of C. Y. (patient with thalassemia) and of a control. The per cents represent the concentration of the solution of sodium chloride present in the respective tubes. Hemolysis was complete for the control at 0.34 per cent and still incomplete for the patient at 0.20 per cent.

16. Bradford, W. L., and Dye, J.: Observations on the Morphology of the Erythrocytes in Mediterranean Disease—Thalassemia, J. Pediat. **9**:312-317 (Sept.) 1936.

17. Barrett, A. M.: A Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, J. Path. & Bact. **46**:603-618 (May) 1938.

18. Stephens, D. J., and Tatelbaum, A. J.: Elliptical Human Erythrocytes, J. Lab. & Clin. Med. **20**:375-383 (Jan.) 1935.

Having discussed the criteria by which the carrier state can be detected, it is fitting that we mention the pitfalls which may lead to erroneous diagnosis. Although the peculiar changes in the hemoglobin values, the erythrocyte counts and the relationships of the hematocrit readings are certainly as fundamental as abnormalities detected on a blood smear, the fact remains that the carrier state is most likely to be confused with conditions in which the smear shows target and oval cells and in which there is also decreased fragility of the erythrocytes in hypotonic solution of sodium chloride.

Target cells were reported in persons with sickle cell anemia (Haden and Evans [19]), with diseases of the liver, after splenectomy and with steatorrhea (Barrett,[17] Dameshek [5]). We observed their presence in persons with obstructive jaundice, Laennec's cirrhosis, catarrhal jaundice and metastatic involvement of the liver. In 1 instance they were also noted in a person with a severely decompensated heart without evidence of hepatic disease other than probable cardiac cirrhosis. We also noted numerous target cells in the blood smear of an elderly white man, not of Mediterranean descent, who had thrombopenic purpura of undetermined cause. There were no clinical grounds to support a diagnosis of hepatic disease. Oddly, in this case there was no evidence of increased resistance of erythrocytes to hypotonic solution of sodium chloride.

Of greater interest was our observation of an apparently normal 30 year old white woman, S. G., who had no Mediterranean background whatsoever but who presented a hematologic picture comparable to that seen in a carrier of thalassemia. This patient had received adequate iron therapy. A careful study of the patient's parents failed to reveal similar abnormalities (table 8). The significance of such cases is not clear. Occasionally, they may offer a serious problem in differential diagnosis. For the most part, however, careful examination will show the presence or the absence of morbid states which may give rise to confusion.

As target cells are sought for more assiduously, more conditions may be found in which they exist. It should be pointed out, however, that target cells, despite speculation to the contrary, have never been demonstrated as a fundamental abnormality in this condition. Their exact significance has never been elucidated satisfactorily. We have noted large and unexplained variations in the numbers of target cells on different sections of the same smear. Barrett [17] recorded a similar observation. It seems likely that differences in the technic of preparation may affect the number of target cells seen. Despite the fact that Barrett [17] and Dameshek [5] showed the target cell to be a thin, resistant cell, changes in fragility may be comparatively slight, even when large numbers of target cells are present in a smear. We noted this in some cases of catarrhal jaundice. This suggests that cells defective in varying degrees may present an identical blood picture. Certainly the presence of target cells in a number of conditions argues against their specificity, and their importance should not be overemphasized. They should be accepted as one of the pegs supporting the diagnosis, but without other supports they form an unstable foundation on which to build an opinion.

It is impossible to estimate what percentage of carriers are not detected because their abnormalities are minimal and cannot be measured by the crude methods now in use. Carriers in families Si. and Sc. did not show such pronounced abnormalities as those in families Y. and Sal. Such persons can be designated as carriers with less certainty than those showing more dramatic hematologic changes. That other carriers may more closely resemble normal persons is a distinct possibility. Further study is necessary before this problem can be elucidated.

TABLE 8.—*Summary of Blood Findings in Family G.*

Name	Age in Yr.	Hemoglobin in Gm. per 100 Cc.	R. B. C. in Millions per Cu. Mm.	Volume Packed R. B. C. in per Cent	Retic. in per Cent	M. C. V. in Cubic Microns	M. C. H. in Micro-micro-grams	M. C. H. C. in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Begins	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent: Complete
S. G., patient.....	26	11.35	4.90	37.8	1.2	77.1	23.2	30.0	2+	3+	0	0.44	0.22
												0.48*	0.32
E. G., mother.....	72	12.25	3.89	40.0	0.2	102.9	31.5	30.6	0	0	0	0.50	0.30
												0.50*	0.34
H. G., father.....	69	12.50	4.18	41.3	0.2	98.9	29.9	30.3	0	0	0	0.48	0.32
												0.48*	0.34

* Control determination.

19. Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in the White Race, Arch. Int. Med. **60**:133-142 (July) 1937.

COMMENT

To the best of our knowledge, thalassemia is the first inherited condition of any medical importance in which it seems possible to detect carriers with a high degree of accuracy. Epilepsy and xeroderma pigmentosum are the only other disorders in which an approach to this state of affairs exists. It has been conclusively demonstrated that in the majority of cases of idiopathic epilepsy, one or both asymptomatic parents exhibit epileptiform brain waves (see Penfield and Erickson [20] for a summary). Siemens and Kohn [21] pointed out that the siblings of persons with xeroderma pigmentosum are often freckled but have no other characteristics suggesting the disease. These investigators suggested that such freckled siblings are genetic carriers of the trait. One may surmise that a hereditary mechanism comparable to the one which seems probable here is in operation. It is to be expected that further search will reveal other conditions of a similar nature. Blood dyscrasias such as sickle cell anemia and familial hemolytic jaundice offer some promise (Dameshek [8]). The possible clinical application of such knowledge in the prophylaxis of the various diseases is so obvious as to require no comment.

The question of terminology for these two closely related conditions has thus far been avoided. It would seem desirable to have names expressing the close pathologic and genetic relationship. Smith [9] referred to both the mild and the severe form of the disease as Mediterranean anemia. However, we propose that the conditions be separated and known as "thalassemia major" and "thalassemia minor." This designation is logical from both the genetic and the pathologic standpoint. Thalassemia major is in most essential respects an exaggeration of thalassemia minor. This is in keeping with the genetic mechanism which has been postulated. The chief well established qualitative difference is the appearance in thalassemia major of circulating erythroblasts, frequently out of all proportion to the degree of the anemia. The significance of this difference is not clear. One could speculate, however, that in thalassemia major the erythroblasts escape into the circulation in the face of chronic demands on a particular type of hyperplastic, inadequate marrow or a marrow with a lowered threshold for the release of erythroblasts. Whipple and Bradford [2] stressed the fact that the pathologic picture of the bone marrow is one of deficiency. The basic defect may thus be regarded as an inherited inability to utilize or synthesize some substance necessary to normal hemopoiesis, this inability being greater in the homozygote than in the heterozygote. Comparable situations have been described in recent years in both plants and animals, and in some instances it has been possible to identify and supply the deficient elements (Beadle and Tatum [22]). Thus far, efforts to identify the missing factor in thalassemia have been entirely unsuccessful.

The time of onset of the carrier condition is unknown at present. Significant changes in the blood of J. Sc. were detected at the age of 1 year. This child is of additional interest because he showed all the features of true mongolism. It is felt that these bear no relationship to the mongoloid feature of thalassemia but are merely coincidental. We consider the future development of full-blown thalassemia in this child unlikely.

Children having thalassemia routinely require repeated transfusions. In most instances the blood is obtained from the patient's parents or other relations. This practice embodies undesirable features from the standpoint of both the donor and the recipient. 1. Frequently the donor's blood is significantly hypochromic, so that the hemoglobin content per hundred cubic centimeters of blood is below the desired optimum. 2. More important, erythrocytes which have the same type of defect inherent in the erythrocytes of the recipient, albeit quantitatively less severe, are being transfused. There is presumptive evidence that such cells are undergoing more rapid destruction than normal erythrocytes, in the body of both the carrier, who is the donor, and the thalassemic recipient. 3. It is undesirable to bleed donors whose hemopoietic apparatus is already overstrained and defective. It seems likely that the supportive value of such transfusions may be significantly reduced. Transfusion from an extraneous normal donor or from a proved normal relative is a more rational procedure.

Lastly, it should be pointed out that the discovery of carriers of thalassemia adds a previously undetected morbid condition to adult medicine and takes thalassemia, in a broad sense, out of the purely pediatric field. Many of these carriers present syndromes which may mimic other diseased states—rheumatic fever,

20. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

21. Siemens, H. W., and Kohn, E.: Studien über Vererbung von Hautkrankheiten: IX. Xeroderma pigmentosm (mit Mitteilung von 5 neuen Fällen), Ztschr. f. indukt. Abstammungs- u. Vererbungsl. **38**:1-16, 1925.

22. Beadle, G. W., and Tatum, E. L.: Genetic Control of Biochemical Reactions in Neurospora, Proc. Nat. Acad. Sc. **27**:499-506, 1941.

lead poisoning, hemolytic jaundice and the splenomegalies. Others, while presenting less definite symptoms, undoubtedly are constitutionally inferior and more susceptible to infections of all sorts. Their detection and diagnosis are a new medical responsibility.

SUMMARY

Hematologic data and pedigrees were collected for the families of 3 patients with thalassemia and 1 with the similar but milder anemia, first described by Wintrobe.[3] These 4 families include a total of 34 persons.

Twenty-four of these persons had hematologic findings qualitatively similar but quantitatively less severe than those of full-blown thalassemia, including increased resistance of erythrocytes to hypotonic solutions of sodium chloride, target and oval red blood cells, microcytosis and hypochromia.

Three possible genetic mechanisms involved in the familial incidence of thalassemia have been reported in the literature. The likelihood of each mechanism is established by the statistical analysis of our data and of those in the literature. The bulk of the evidence, with one significant departure, favors the hypothesis that the mild state is due to heterozygosity for a factor which when homozygous results in full-blown thalassemia.

It is suggested, on the basis of the pathologic and genetic evidence, that the full-blown disease be designated "thalassemia major" and the milder carrier state "thalassemia minor."

In the differential diagnosis of thalassemia minor the chief diseases to be considered are: iron deficiency anemia, the splenomegalies, lead poisoning, rheumatic fever and conditions, such as hepatic disease, in which many target cells may be present.

Certain cases of familial ovalocytosis in Mediterranean peoples may be instances of thalassemia minor.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Concluded from page 152)

GRANULOCYTOPENIA AND AGRANULOCYTOSIS

Leukemoid Reactions.—One case of osteopetrosis and 17 cases of myelofibrosis are reported by N. Rosenthal and Erf,[358] with a discussion of the clinical and hematologic features and differential diagnosis of these conditions. Osteopetrosis occurs most often in childhood and is commonly associated with congenital abnormalities, mental retardation and usually enlargement of the liver and spleen. There is a generalized condensation of bone. Anemia is progressive and is usually associated with thrombopenia and leukopenia. Often immature cells of the myeloid series are seen in the peripheral blood. Myelofibrosis was first described by Hueck in 1879; since then approximately 75 cases have been reported. The diagnosis of the condition is generally made at autopsy. The clinical features include weakness, dyspnea, refractory anemia, splenomegaly, periostitis and pains in the bones. Myelofibrosis is observed equally often in the two sexes and has no predilection for any age group. The course of the disease may be acute or exceedingly chronic. The blood picture is often like that of chronic myelogenous leukemia and is sometimes similar to that of osteopetrosis. Myelofibrosis must be differentiated from other leukemoid reactions and from conditions associated with splenomegaly. Sternal aspiration and biopsy are helpful in the diagnosis, the marrow usually being gritty and hypocellular. Splenic puncture frequently reveals myeloid metaplasia, and lymph node puncture may show the same condition. Changes in bones which may suggest the diagnosis are apparent by roentgen examination in about a third of the cases. The cause and mode of origin of myelofibrosis are unknown. The condition may be secondary to loss of function of the bone marrow, similar to that occurring in cases of "spent" polycythemia. Blood transfusion is the only beneficial form of treatment. Splenectomy is contraindicated.

Mendeloff and J. Rosenthal[359] report the case of a man of 57 years in whom anemia preceded roentgen evidence of osteosclerosis. The patient's spleen had been removed five years before the signs of increased density of the bones developed, and a diagnosis of questionable Hodgkin's disease had been made on histologic grounds. The authors infer that the sclerosis was secondary and present only in the later stage of an idiopathic progressive refractory anemia. Pavlovsky[360] emphasizes the importance of differentiating between compensatory myeloid metaplasia of the spleen in aplastic states of the bone marrow and chronic myelogenous leukemia. He observed 7 cases of the former and 99 cases of the latter. Aspiration of sternal marrow and splenic puncture are valuable diagnostic procedures in suspected cases of myeloid metaplasia. The effects of irradiation therapy on patients with this condition are harmful, and rapidly developing anemia, leukopenia and thrombopenia may be provoked by such treatment. Rusakor[361] reports 4 cases of sclerosis accompanied by changes in the blood indicative of leukemia, associated with myeloid metaplasia. The author suggests the term "osteomyelopoietic dysplasia" for this condition. The formation of bone is disordered, and a specific pathologic type of osteogenesis is evident.

Two patients, a girl of 8 years and a boy of 1 year, with extreme leukocytosis are reported on by Chaudhuri.[362] The former had a leukocyte

358. Rosenthal, N., and Erf, L. A.: Clinical Observations on Osteopetrosis and Myelofibrosis, Arch. Int. Med. **71**:793 (June) 1943.

359. Mendeloff, J., and Rosenthal, J.: Leukoerythroblastic Anemia with Diffuse Osteosclerosis, Ann. Int. Med. **19**:518, 1943.

360. Pavlovsky, A.: Compensatory Myeloid Metaplasia of the Spleen: Importance of Differentiation from Chronic Myeloid Leukemia, Medicina **3**:287, 1943.

361. Rusakor, A. V.: Osteosclerosis and Leukemia, Klin. med. **20**:32, 1942.

362. Chaudhuri, K. C.: Pseudoleukaemic Reaction in Children with Report of Two Cases, Indian J. Pediat. **10**:14, 1943.

count of 95,000 cells per cubic millimeter with a neutrophil percentage of 96 in association with a positive Mantoux reaction. The second patient had a leukocyte count of 40,000 cells per cubic millimeter with a normal differential count, attributable to an attack of diarrhea caused by a protozoal infection. Marino [363] discusses pseudoleukemia of the von Jaksch type and considers it a manifestation of a constitutional defect of the hemopoietic organs. Schultz [364] reports 3 cases of severe leukemoid reactions (leukanemia) occurring soon after parturition. The changes in the blood were not due to sepsis and included severe macrocytic anemia with the appearance of megaloblasts, erythroblasts and young myeloid cells in the blood stream. Fraser [365] observed a man of 39 years in whom there developed lymphocytosis, the lymphocytes amounting to 84 per cent of a leukocyte value of 114,000 per cubic millimeter, associated with generalized pruritus and a burning sensation of the skin and exfoliative dermatitis. Biopsies of lymph nodes revealed chronic nonspecific lymphadenitis, and sternal aspiration supplied no evidence of leukemia. General irradiation of the body of the Heublein type together with regional roentgen therapy was followed by apparently complete clinical and hematologic recovery. A case of eosinophilic leukocytosis in a man of 40 years is reported by Tecoz and his associates.[366] Since no cause for the eosinophilia was found, the authors designate the condition as an essential eosinophilia of pseudoleukemic type. Because of the persistent symptoms of fatigue, enlargement of the lymph nodes and spleen and elevated sedimentation rate, it appears to us that this patient may have had Hodgkin's disease.

Experimental Studies on Leukemia.—A further report of experiences with urinary substances capable of affecting hemopoiesis in experimental animals is given by Miller and Turner.[367] They describe their method of preparing concentrates from the urine and feces of patients with leukemia, and state that each of the two active materials obtained, one possessing lymphoid and the other myeloid stimulating activity, may be converted into the other. Although with the amounts employed no activity was demonstrated in the extracts of urine from healthy persons, the authors assume that the body fluids of such persons contain substances which act as regulators of normal hemopoiesis. They suggest that such substances are mutually reciprocal in action and that the myeloid substance stimulates myeloid proliferation without maturation. The maturation of cells of the myeloid series is induced by the action of the lymphoid substance through inhibition of the proliferation of these cells. A corresponding role is played by the lymphoid and myeloid substances respectively with regard to the proliferaton and maturation of cells of the lymphoid series. In normal circumstances the balanced action of the two substances is believed to regulate hemopoiesis. In chronic forms of leukemia it is thought that one substance is present in excess, stimulating proliferation, while the other is available in normal amounts, thereby enabling maturation to occur. The acute leukemias may be explained, according to the authors, by an excess of one stimulating substance and a deficit of the other. Although histologic evidence is presented in support of these views, a large part of the conclusions and hypotheses of the authors is highly speculative.

The retention of radioactive phosphorus in leukemic patients, according to S. Warren,[368] is relatively constant, amounting on the third day after intravenous administration to 75 per cent of the original dose and on the seventh day to 52 per cent. The rate of excretion does not vary significantly with alteration of doses within the therapeutic range or with the clinical condition of the patient. When the intravenous route is used only a neglible amount of the radioactive phosphorus is excreted in the feces.

Claude and Potter,[369] by a method of extraction and centrifugation, were able to isolate the chromatin strands from the nuclei of leukemic cells, and they present evidence that in resting cells such threads are related to if not identical with the chromosomes.

363. Marino, A. A.: A proposito de un caso de anemia pseudo-leucémica, Rev. de med. y cir., Barranquilla **10**:13, 1943.

364. Schultz, W.: Ueber Leukanämie im Wochenbett mit Ausgang in Heilung und über Beziehungen zwischen Leukanämie und Leukämie, Deutsche med. Wchnschr. **68**:1238, 1942.

365. Fraser, J. F.: Exfoliative Dermatitis with a Leukemoid Blood Picture Indistinguishable from Lymphatic Leukemia, Arch. Dermat. & Syph. **48**:42 (July) 1943.

366. Tecoz, R. M.; de Weck, L., and Fröhner: Eosinophilie, leucocytose éosinophilique, éosinophilie pseudo-leucémique, Helvet. med. acta **10**:17, 1943.

367. Miller, F. R., and Turner, D. L.: The Action of Specific Stimulators on the Hematopoietic System, Am. J. M. Sc. **206**:146, 1943. Turner, D. L., and Miller, F. R.: Preparation of Concentrates of Specific Substances from Urine and Feces in Leukemia, J. Biol. Chem. **147**:573, 1943.

368. Warren, S.: The Retention of Radioactive Phosphorus in Leukemic Patients, Cancer Research **3**:872, 1943.

369. Claude, A., and Potter, J. S.: Isolation of Chromatin Threads from the Resting Nucleus of Leukemic Cells, J. Exper. Med. **77**:345, 1943.

The known effect of menadione (2-methyl-1,4 naphthoquinone) in reversing the increase in aerobic glycolysis induced by potassium arsenite led C. O. Warren [370] to hope that menadione would counteract the effects of arsenite on normal but not on leukemic cells. Leukemic material from both mice and human beings was employed, but no such differential action was observed. Glutathione, likewise, was ineffective in preventing or counteracting the influence of arsenite on the respiration and motility of marrow cells.

Potter and his associates [371] studied preleukemic changes in the tissues of mice of a strain susceptible to spontaneous leukemia and observed restricted areas of reticulum hyperplasia occurring in the medullary spaces of the lymph nodes and the perivascular regions of the liver. When freely circulating malignant lymphocytes were produced by the animals, the majority of the widespread lesions common to the terminal stages of leukemia were accounted for by invasion.

McEndy, Boon and Furth [372] produced leukemia in mice by repeated percutaneous application of methylcholanthrene. The animals were killed at intervals, the blood-forming organs examined microscopically and transmission experiments made with a suspension of cells from the spleen and lymph nodes. Numerous transmission experiments made before the eighth week of painting gave uniformly negative results, although hyperplastic changes were evident in lymphoid tissues. In 3 instances leukemia was first demonstrated by transmission experiments. This procedure applied in cases of histologically definite leukemia failed in only 1 of 46 inoculated mice. The type of leukemia was either lymphoid or atypical except for a few instances of myeloid and monocytic leukemia. The atypical cells appeared to originate in the lymphoid tissues. The incidence of leukemia was slightly higher among mice treated with roentgen rays and painted than among animals painted but not irradiated. The majority of induced leukemias are manifested by specific changes in the blood at least two weeks before death.

Burk and his colleagues [373] studied the metabolism of tissue from lymph nodes, spleen and liver obtained from mice in which leukemia had been induced. Lymphoid, myeloid, monocytic and atypical forms of leukemia were represented. They concluded that the metabolism of these cells, while qualitatively characteristic of cancer, probably represents, together with certain chicken erythroleukoses, the lowest limit for any type of malignant tissue reported to date. Likewise, the metabolism of most spontaneous mouse leukemias is only moderately malignant. The less striking metabolism of these highly malignant blood cells, in contrast with the metabolism of most malignant tumor aggregates, is possibly in some way related to their highly diffuse circulating systemic nature, which introduces factors, as yet unrecognized, that reduce comparability.

Furth and Boon [374] found that the leukemogenic action of small doses of methylcholanthrene was greatly enhanced by preirradiation with doses of roentgen rays which alone rarely produce leukemia. Flory and his associates [375] concluded that no organic or benzene derivative was as effective as potassium arsenite or benzene in prolonging the life of leukemic mice. Underfeeding alone retarded the development of most strains of leukemia, but many of the chemicals tested seemed to exert their beneficial effects without causing loss of weight. Great differences were observed in the effect with various strains of mice as well as with the types of leukemia tested. Sulfadiazine and sulfaguanidine administered to leukemic mice had neither a beneficial nor a deleterious effect.

Methylcholanthrene and benzpyrene were injected subcutaneously into rats by Dunning and Reich,[376] who observed frequently an initial increase in erythrocyte and leukocyte values followed by a decline in red blood cells and hemoglobin. The white cell count remained elevated, with an especially marked increase in the monocytes.

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370. Warren, C. O.: The Effects of Potassium Arsenite (Fowler's Solution) on the Respiration and Glycolysis of Normal and Leukemic Tissues, with Observations on the Action of Menadione, 2-Methyl-1,4 Naphthoquinone, Am. J. Physiol. **139**:719, 1943.

371. Potter, J. S.; Victor, J., and Ward, E. N.: Histological Changes Preceding Spontaneous Lymphatic Leukemia in Mice, Am. J. Path. **19**:239, 1943.

372. McEndy, D. P.; Boon, M. C., and Furth, J.: Induction of Leukemia in Mice by Methylcholanthrene and X-Rays, J. Nat. Cancer Inst. **3**:227, 1942.

373. Burk, D.; Sprince, H.; Spangler, J. M.; Boon, M. C., and Furth, J.: Metabolism of Induced and Spontaneous Leukemias in Mice, J. Nat. Cancer Inst. **3**:249, 1942.

374. Furth, J., and Boon, M. C.: Enhancement of Leukemogenic Action of Methylcholanthrene by Pre-Irradiation with X-Rays, Science **98**:138, 1943.

375. Flory, C. M.; Furth, J.; Saxton, J. A., Jr., and Reiner, L.: Chemotherapeutic Studies on Transmitted Mouse Leukemia, Cancer Research **3**:729, 1943.

376. Dunning, W. F., and Reich, C.: Studies on Morphology of Peripheral Blood of Rats: Rats Injected Subcutaneously with Carcinogenic Hydrocarbons, Cancer Research **3**:258, 1943.

Murphy and Sturm [377] state that sodium pentobarbital, paradichlorobenzene, amyl acetate and sovasol (a "close-cut, highly purified naphtha") all possess leukemia-inciting properties when given to susceptible mice. Also, they all decreased the resistance to transmissible rat leukemia, but the authors' experiments showed that there were great variations, which may, in fact, have been seasonal. The authors believe that induced resistance to leukemia may be a type of sensitization reaction and that agents interfering with the manifestations of the phenomenon act by suppression of the response of the animal. They conclude that if it can be shown that inciters suppress resistance it may indicate that they act not by direct effect on the cells but by the release of a natural tendency.

According to Hall and Pollard,[378] injection of leukosis blood by the intravenous route into 2,656 chick embryos during thirty serial passages resulted in the development of leukosis in 1,089 (41 per cent), either in the embryonic stage or within a week after hatching. Of the total number of embryos inoculated, 621 (23.3 per cent) hatched, and of those hatching 389 (62.6 per cent) died of leukosis. The average incubation period and course of the disease in the embryos was seven and four-tenths days, whereas for the chicks which hatched the average period was fourteen and eight-tenths days. There was no evidence of change in virulence in the leukosis-producing agent as a result of serial passages, and no evidence of alteration in the nature of the hemopoietic response.

Opie [379] reviews the subject of experimental induction of leukemia in mice by means of carcinogenic agents, including hydrocarbons and roentgen rays, and comments on the transmissibility of these leukemias. He states that there is suggestive evidence that chemical and physical agents may produce chronic leukemia in human beings. Leukemia following exposure to benzene and the apparently higher incidence of the disease among roentgenologists and persons exposed to radioactive substances are mentioned, but the author states that no available statistical procedure serves to eliminate the possibility of coincidence in relation to the disease and its assumed cause. There is little evidence, according to Opie, that trauma is a cause of leukemia. Gorer [380] also reviews the present status of experimental transmissible leukemia and considers the analogy it presents to human leukemia. He emphasizes the importance of cultures of leukemic tissue.

Polycythemia.—Two cases of polycythemia associated with hemangioblastoma are reported by Carpenter and his associates.[381] In neither case was there leukocytosis, reticulocytosis or enlargement of the liver or spleen. The erythrocyte values became normal after surgical removal of the tumors. The authors believe that these cases are instances of symptomatic polycythemia of neurogenic origin. Tinney, Hall and Giffin [382] analyzed the data on 163 cases of polycythemia vera observed at the Mayo Clinic with respect to the incidence of peptic ulcer, the status of the liver and spleen, the association of cardiac disease and hypertension, the hematologic complications and the manifestations in the central nervous system. These communications are essentially summaries of statistical data, and it is not possible to present a recapitulation of the observations in this review. One important conclusion of the authors is that when the blood volume has been reduced to normal in patients with polycythemia the cerebral manifestations improve except in those instances in which brain tissue has been injured by hemorrhage or thrombosis. If the cerebral manifestations progress despite treatment, a mass-expanding lesion should be suspected.

Stoger [383] submits evidence derived from a single clinical experiment in support of his view that polycythemia vera is caused by an increase in the gastric secretion of Castle's intrinsic factor, due to a disturbance in the central nervous system regulation of hemopoiesis. His experiment consisted of determining the hematologic response of an untreated patient with pernicious anemia to the administration, during successive periods, of gastric juice obtained from a normal person and from a patient with polycythemia.

377. Murphy, J. B., and Sturm, E.: Effect of Sodium Pentobarbital, Paradichlorbenzene, Amyl Acetate, and Sovasol on Induced Resistance to a Transplanted Leukemia of Rat, Cancer Research **3**:173, 1943.

378. Hall, W. J., and Pollard, M.: Further Studies on the Propagation of Fowl Leucosis in Chick Embryos by Intravenous Inoculation, Am. J. Vet. Research **4**: 287, 1943.

379. Opie, E. L.: The Experimental Production of Leukemia and Its Significance in Relation to the Human Disease, Proc. Inst. Med. Chicago **14**:382, 1943.

380. Gorer, P. A.: Experimental Studies on Leukemia and Allied Conditions, Guy's Hosp. Gaz. **57**:166, 1943.

381. Carpenter, G.; Schwartz, H., and Walker, A. E.: Neurogenic Polycythemia, Ann. Int. Med. **19**:470, 1943.

382. Tinney, W. I.; Hall, B. E., and Giffin, H. Z.: Polycythemia Vera and Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **18**:24, 1943; The Liver and Spleen in Polycythemia Vera, ibid. **18**:46, 1943; Cardiac Disease and Hypertension in Polycythemia Vera, ibid. **18**:94, 1943; Hematologic Complications of Polycythemia Vera, ibid. **18**:227, 1943; Central Nervous System Manifestations of Polycythemia Vera, ibid. **18**:300, 1943.

383. Stoger, R.: Beitrag zur Pathogenese der Polycythaemia Vera, Klin. Wchnschr. **22**:342, 1943.

The gastric juice was obtained after histamine stimulation and was incubated with beef before being given to the patient. Franke [384] concluded from his observation of the response of a patient with pernicious anemia to the administration of blood obtained from a patient with polycythemia that in the latter disease the blood does not contain the anti-pernicious-anemia factor.

Medinger and Craver [311] treated 5 patients with polycythemia, 2 of whom had associated chronic myelogenous leukemia, with irradiation of the whole body and concluded that the results were not superior to those previously obtained in the same patients by means of local therapy over the long bones, sternum and vertebrae. Reznikoff and Carty [385] report their experience with generalized irradiation in 22 cases of polycythemia vera. The results obtained were apparently as satisfactory as those previously reported from the administration of radioactive phosphorus. Erf and Jones [386] consider that radioactive phosphorus is the most convenient and satisfactory agent for the treatment of polycythemia and its associated manifestations. Their experience was derived from the treatment of 11 patients with this disease, in all of whom satisfactory remissions were obtained.

Herzog [387] reports his results from the treatment of polycythemia with diets low in animal protein and vitamins. According to him, 17 of 19 patients so treated experienced a remission of their disease. The effects are attributed to an induced deficiency of the extrinsic factor. Hines and Darnall [388] advocate the withdrawal of 200 to 250 cc. of blood at one to two week intervals from patients with polycythemia until the computed excess of erythrocytes has been removed. Check-up examinations should then be done bimonthly. It is stated that by this method of venesection there occurred much less secondary stimulation of erythropoiesis than when large amounts of blood, such as 1,500 cc. in fourteen days, were removed.

384. Franke: Ist die Polycythaemia Vera das positive Gegenstück der Biermerschen Anämie? Klin. Wchnschr. **22**:434, 1943.

385. Reznikoff, P., and Carty, J. R.: General Body Irradiation (Spray) in Polycythemia Vera and Chronic Leukemia, Tr. A. Am. Physicians **57**:241, 1942.

386. Erf, L. A., and Jones, H. W.: Radio Phosphorus—An Agent for Satisfactory Treatment of Polycythemia and Its Associated Manifestations: Report of Case of Polycythemia Secondary Possibly to Banti's Syndrome, Ann. Int. Med. **19**:587, 1943.

387. Herzog, F.: Die Behandlung der Polyglobulie durch Vitaminentzug, Klin. Wchnschr. **22**:366, 1943.

388. Hines, L. E., and Darnall, W. C.: The Control of Polycythemia Vera by Venesection, Am. J. M. Sc. **206**:434, 1943.

The case of a man of 73 years in whom macrocytic anemia and neutrophilic leukocytosis associated with carcinoma of the tongue developed nine years after he had received treatment for polycythemia with phenylhydrazine is reported by Ziady.[389] Hansen-Pruss and Goodman [390] report on 2 patients, 1 of whom acquired monocytic leukemia of the Schilling type and the other acute myeloblastic leukemia while receiving spray irradiation for the treament of polycythemia vera.

Multiple Myeloma.—The nature of the serum and urinary proteins in 7 cases of multiple myeloma was investigated by Moore, Kabat and Gutman,[391] employing correlated salting-out, electrophoretic and ultracentrifugal technics, supplemented in 2 cases by immunologic methods. They conclude that in many and probably in the majority of cases of multiple myeloma with hypoproteinemia only a small proportion of the increase in protein is of Bence Jones type, although marked Bence Jones proteinemia does occur in some cases. Shapiro, Ross and Moore [392] describe a viscous protein obtained from the serum of a patient with multiple myeloma. Keilhack [393] has also studied the disturbance in serum proteins in 2 patients with multiple myeloma and in 1 with plasma cell leukemia. Spontaneous clumping of the red cells led to the making of an early diagnosis in both of the cases of multiple myeloma. Brunner [394] found gross disturbances in protein metabolism associated with reactions of the plasma cells of the marrow. He states that the function of the plasma cells of the marrow is closely connected with the formation of the plasma proteins and that the reaction of these cells is essentially the same in neoplastic and in defensive reactions but that in the latter changes may be too small to be detected.

389. Ziady, F.: A Case of Polycythaemia with Subsequent Anaemia, Clin. Proc. **2**:130, 1943.

390. Hansen-Pruss, O. C., and Goodman, E. G.: Acute Leukemia as a Terminal Event in Polycythemia Vera: Report of Two Cases with Autopsies, North Carolina M. J. **4**:254, 1943.

391. Moore, D. H.; Kabat, E. A., and Gutman, A. B.: Bence-Jones Proteinemia in Multiple Myeloma, J. Clin. Investigation **22**:67, 1943.

392. Shapiro, S.; Ross, V., and Moore, D. H.: A Viscous Protein Obtained in Large Amount from the Serum of a Patient with Multiple Myeloma, J. Clin. Investigation **22**:137, 1943.

393. Keilhack, H.: Ueber die Störungen des Eiweissstoffwechsels beim multiplen Myelom, und bei der Plasma Zellenleukämie, Deutsches Arch. f. klin. Med. **191**:36, 1943.

394. Brunner, W.: Ueber die plasmocytäre Reaktion des Knochenmarks, das Plasmocytom Myelom und das solitäre Plasmocytom, Deutsche Ztschr. f. Chir. **257**:718, 1943.

In discussing the diagnosis of multiple myeloma Schupbach [395] states that the older diagnostic triad of pain and brittleness of bones, cachexia and Bence Jones proteinuria is found in only about one half of the cases of multiple myeloma. He reports 2 cases of the disease and comments that irradiation therapy is of value in the relief of pain but that it has no effect on the hyperproteinemia with increase of globulin characteristic of the disease.

Medinger and Craver [311] report their observations on the effect of irradiation therapy on 11 patients with multiple myeloma. Four of the patients survived for periods of two to five years after the institution of therapy. Although positive conclusions could not be drawn, it appeared to the authors that irradiation of the entire body may materially increase the duration of life.

Beyer [396] reports a case of plasmocytoma in a man of 65 years in whom there was involvement of one clavicle and one rib. The tumor in the clavicle was removed by excision, and the neoplasm in the rib regressed spontaneously during a two year period of observation. Toth and Wintermantel [397] observed a long period of survival in a woman with multiple myeloma involving the pubic bone which was treated by irradiation. Francisco [398] reports a case of the disease in a mulatto woman of 41 years. McDonald [399] reports an instance of rapid progress of multiple myeloma with early renal failure and uremia. Schindler [400] observed a case of infiltration of the sinusoids of the liver by myelomatous tissue with prothrombin deficiency and generalized bleeding. A case of multiple myeloma with involvement of the larynx is reported by Pearson and his associates.[401]

Bone Marrow.—It is remarkable, in view of the wide interest in neoplastic alterations of the leukopoietic tissues that so few observations have been reported on similar changes affecting the precursors of the erythrocytes. Recently, however, an increasing awareness of the existence of such malignant erythroblastic conditions has become apparent. Some communications dealing with the subject are reviewed in the sections on leukemia and polycythemia. Others are included in this section.

Most extensive studies of the marrow in erythroblastoma as well as in a number of other malignant and nonmalignant conditions have been reported by Kienle,[402] based on his observations of marrow removed by aspiration in 1,400 cases. He describes the case of a 10 year old girl with "erythroblastic leukemia" in whom hyperplastic and disordered erythropoiesis was observed in the marrow together with histoid hyperplasia and many hemohistioblasts. Sternal aspiration was found to render valuable assistance in the differential diagnosis of erythroblastemic conditions. In polycythemia vera an increase in megakaryocytes is found in the marrow, whereas this is not the case in secondary polycythemias. In localized tuberculosis of the spleen and in lymphogranulomatosis erythroblastemia may be observed. The author offers an orderly system of presentation of the erythroblastoses and erythroleukemias. Kienle [403] discusses the types of mitosis observed in the cells of the marrow of 1,400 patients examined by sternal puncture. His conclusions follow. Hemocytoblasts seldom show mitosis in either normal or leukemic forms. In myeloblasts many more prophases than metaphases or telophases are observed, but in promyelocytes the end phases are more numerous. Characteristic chromosome separations and multipolar mitoses may be seen in myeloblasts and promyelocytes. The mitoses of normal erythroblasts are described and contrasted with the many types of atypical and multipolar divisions of the erythroblast which are observed in cases of acute erythremia, severe lead anemia, severe anemia due to infection or intoxication, hemolytic icterus and essential thrombopenia (purpura hemorrhagica). Their presence is always an indication of high grade injury of the bone marrow. The hitherto unanswered question of the existence of amitotic division of the erythroblast was decided in the affirmative. Examination of the marrow in more than 100 cases of severe anemia demonstrated the presence of amitotic erythroblastic division in states of most severe exhaustion of the bone marrow. In erythremia pseudoamitotic divisions

395. Schupbach: Multiples Myelom, Praxis **321**:220, 1943.

396. Beyer, G.: Zur Frage der Spontanheilung eines malignen Myeloma, Zentralbl. f. Chir. **69**:781, 1942.

397. Toth, B. J., and Wintermantel, J. A.: An Apparently Solitary Myeloma of Bone with Subsequent Generalization: Favorable Response to Irradiation with Unusual Reactions, Radiology **41**:472, 1943.

398. Francisco, R.: Myelomatosis, Bol. Asoc. méd. de Puerto Rico **35**:284, 1943.

399. McDonald, R. H.: Multiple Myeloma with Nitrogen Retention, Cleveland Clin. Quart. **10**:36, 1943.

400. Schindler, J. A.: A Case of Multiple Myeloma with Liver Infiltration and a Low Prothrombin Purpura, Ann. Int. Med. **19**:140, 1943.

401. Pearson, B.; Stark, E., and Kepl, M.: Multiple Myeloma with Laryngeal Involvement, Arch. Path. **36**: 321 (Sept.) 1943.

402. Kienle, F.: Die Leistungsfähigkeit der Sternalpunktion in der Differentialdiagnose von Erythroblastamien, Med. Klin. **38**:101, 1942.

403. Kienle, F.: Ueber Knochenmarksfunktion im Lichte der Sternalpunktion; die Differentialdiagnose der Mitosen, Amitosen und Pseudoamitosen des Knochenmarkes, Folia haemat. **67**:101, 1943.

of the erythroblasts were recognized. The mitoses of both orthochromic and immature megaloblasts are described and contrasted with those of erythroblasts. Tripolar divisions were observed in basophilic megaloblasts, and such cells, in contradistinction to previous reports, were seen to exhibit splitting off of chromosomes. In cases of severe pernicious anemia amitotic division of basophilic megaloblasts was observed. The differential diagnosis of megaloblast mitosis is not difficult except in special cases, as in the young cells of the erythropoietic series with marrow chromosomes occurring in cases of erythremia. Mitoses are described in granular hemohistioblasts and in plasma cells of healthy marrow. The mitoses of foreign cells invading the marrow, such as lymphogranulomatosis cells and the elements constituting the micrometastases of giant cell sarcoma, are described. It was found that following mitotic nuclear division the cells as a whole failed to separate, thereby giving rise to multinuclear giant sarcoma cells.

Japa [404] analyzed the mitotic activity of human bone marrow, using sternal puncture and a combination of acetocarmine and panchromatic staining methods, in 3 normal persons. The number of dividing cells in normal marrow was found to be 15 per thousand nucleated cells. The proportions of the respective mitotic stages in normal bone marrow were as follows: 40 prophases, 45 metaphases, 60 anaphases and 5 telophases. The proportion of dividing leukoblasts and erythroblasts per hundred mitoses was about 45 and 55 respectively. In the leukoblastic system 97 per cent of dividing cells consisted of myelocytes and 3 per cent of myeloblasts. In the erythroblastic system 91 per cent of dividing cells were late and 9 per cent early erythroblasts. In normal bone marrow dividing multinuclear giant cells were seen.

Limarzi and Levinson [405] describe the case of a man of 77 with myeloid changes indicative of erythroblastoma. The abnormal cells of the erythrocyte series exhibited multipolar mitotic division, and multinuclear and giant forms were present. These elements appeared to arise directly from the reticulum and, together with normal erythroid cells, constituted about 95 per cent of all the cellular elements of the marrow. The authors believe that their observations support the view that there are independent types of erythropoiesis with cells developing along separate lines in the marrow in pernicious anemia in relapse. They explain the rapid change from a megaloblastic to a normoblastic reaction during early induced remission in pernicious anemia as due to the occurrence of multipolar mitoses and division of multinucleated erythroblasts. Jones [406] presents a review of the megaloblast question and draws the rather dogmatic conclusion, not wholly supported by the evidence which he offers, that the megaloblastic series is pathologic and represents neither a return to embryonic conditions nor an arrest of maturation in cells normally present in the marrow of adults.

Kienle [407] reviews the literature on changes in the marrow occurring during infections and intoxications. He presents data with reference to the evolution and maturation of the leukopoietic system derived from the study of 100 cases by sternal aspiration. He concludes that the shift toward more mature forms is a good prognostic sign. In conditions associated with intoxication an increase in the proportion of younger myeloid elements is evidence of decreased maturation in the presence of normal, decreased or increased proliferation. The fact that maturation, proliferation and release of granulocytes need not occur as parallel processes explains the changes of the marrow pattern in various infectious and toxic conditions.

De Paula e Silva [408] discusses the changes in development of granulocytes occurring in hyperchromic anemias and states that liver extract or the antianemic substance exerts a direct effect in this process at the mesenchymatous or hemohistioblastic stage.

A case of metastatic carcinoma involving the skull, with the primary lesion presumably in the prostate, is reported by Miller,[409] who observed a plasmocytic reaction in marrow obtained from the manubrium. Morales [410] reports 2 cases of chloroma of myeloblastic type.

Magyar [411] emphasizes the diagnostic value of sternal puncture and reports 3 cases, 1 each of

404. Japa, J.: A Study of the Mitotic Activity of Normal Human Bone Marrow, Brit. J. Exper. Path. **23**:272, 1942.

405. Limarzi, L. R., and Levinson, S. A.: An Undescribed Type of Erythropoiesis Observed in Human Sternal Marrow, Arch. Path. **36**:127 (Aug.) 1943.

406. Jones, O. P.: Morphologic, Physiologic, Chemical and Biologic Distinction of Megaloblasts, Arch. Path. **35**:752 (May) 1943.

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408. de Paula e Silva, J.: Alteracoes dos granulocitos nas anemias hipercromicas; sen valor para o diagnostico da anemia perniciosa, São Paulo med. **15**:183, 1942.

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410. Morales, L. M.: Sobre dos casos de chloroma en el adulto, Rev. méd. cubana **54**:568, 1943.

411. Magyar, I.: Die Erkenntnis von Erkrankungen mit Hilfe der Sternalpunktion, Klin. Wchnschr. **21**:996, 1942.

malaria, multiple myeloma and Gaucher's disease, in which the correct diagnosis was established by this procedure. Litwins [412] describes a new type of needle for sternal aspiration, which possesses a two way valve. Turkel and Bethell [413] describe and report on the use of a new instrument for obtaining biopsy specimens of marrow. The procedure is simple to carry out, requires no incision of the skin and is practically painless. This device is also well suited to the administration of fluids through the bone marrow. Meyer and Perlmutter [414] found that the circulation time was essentially the same as determined by the saccharin test whether the median basilic vein or the sternal marrow was employed as the route of administration.

Cell values of the bone marrow of monkeys living in a natural habitat are reported by Suarez and his associates.[415] They found that the cell pattern of macacus rhesus monkeys was similar to that of human beings except for a higher proportion of lymphocytes in the marrow of monkeys at all ages. Meyer and Bloom [416] determined the total nucleated cell count and the cellular distribution in marrow removed from the crest of the ilium of dogs. Pachmilewitz and Rosen [417] describe a method of culturing the tibial marrow of rabbits. Maturation of precursors of leukocytes and erythrocytes was observed. Warren [418] studied the respiration glycolysis of the femoral marrow of rabbits and found that myeloid, but not erythroid, cells possessed many of the metabolic properties of cancer cells.

SPLENIC DISORDERS

Sen Gupta [419] reports 50 cases of splenomegaly associated with a slightly macrocytic anemia, reticulocytosis and, frequently, leukopenia and hyperbilirubinemia. The cause of this syndrome, which is prevalent in Bengal, is not known, but an infectious agent is suspected.

Von Gierke's disease (glycogenosis) was encountered in a 14 month old infant by Manter and Bowman.[420] Anemia was present during life, and at postmortem study the presence of glycogen disease of the hepatomegalic type was established.

The hematocrit value and hemoglobin concentration of erythrocytes in splenic blood were determined by Watson and Paine [421] before and after injection of epinephrine into the splenic artery. The majority of the 9 patients studied had an increase in the hematocrit value of the blood from the splenic vein in conjunction with a reduced hemoglobin concentration of the red cells. An actual loss of hemoglobin from the erythrocytes during their sequestration in the spleen was suggested. A decreased resistance to hypotonic solution of sodium chloride, as well as a more spherical form of the cells in the splenic vein, was observed in the single case in which these determinations were made.

Kienle and Malamani [422] noted an increase in the erythrocyte count in the blood of the splenic vein in dogs after intravenous administration of epinephrine. The leukocyte count remained fairly constant, although an increase occurred in monocytes and lymphocytes. Lewis, Werle and Wiggers [423] observed splenic contraction in dogs during hemorrhage. Stephens [424] found that vasodilating drugs, such as amyl nitrite and glyceryl trinitrate, produced contraction of the spleen in cats and dogs. The fact that contraction did not occur if the spleen was first denervated led the authors to the conclusion that the

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413. Turkel, H., and Bethell, F. H.: Biopsy of Bone Marrow Performed by New and Simple Instrument, J. Lab. & Clin. Med. **28**:1246, 1943.

414. Meyer, L. M., and Perlmutter, M.: Absorption Rate from Bone Marrow, Am. J. M. Sc. **205**:187, 1943.

415. Suarez, R. M.; Diaz-Rivera, R. S., and Hernandez-Morales, F.: Aspirated Bone and Marrow Studies in Normal Macacus Rhesus Monkeys, Am. J. M. Sc. **205**:581, 1943.

416. Meyer, L. M., and Bloom, F.: The Bone Marrow of Normal Dogs, Am. J. M. Sc. **206**:637, 1943.

417. Pachmilewitz, M., and Rosen, A.: Studies on Bone Marrow in Vitro: The Cellular Pattern and Behavior of Explanted Bone Marrow, Am. J. M. Sc. **206**:17, 1943.

418. Warren, C. O.: Tissue Metabolism Studies on Bone Marrow: Consideration in Relation to Tumor Metabolism, Cancer Research **3**:621, 1943.

419. Sen Gupta, P. C.: "Bengal Splenomegaly": A Study of Fifty Cases with a Discussion of Aetiology, Indian M. Gaz. **78**:371, 1943.

420. Manter, W. B., and Bowman, R. O.: Von Gierke's Disease (Glycogen Disease of Hepatomegalic Type), Am. J. Dis. Child. **66**:404 (Oct.) 1943.

421. Watson, C. J., and Paine, J. R.: The Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, Tr. A. Am. Physicians **57**:249, 1942; A Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, Am. J. M. Sc. **205**:493, 1943.

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423. Lewis, R. N.; Werle, G. M., and Wiggers, C. J.: Behavior of Spleen in Hemorrhagic Hypotension and Shock, Am. J. Physiol. **138**:205, 1943.

424. Stephens, J. G.: Effects of Vaso-Dilator and Vaso-Constrictor Substances on Normal and Denervated Spleens, J. Physiol. **99**:127, 1940.

effects of such drugs on the spleen were secondary to the fall in blood pressure.

The weight of the spleens of dogs removed while the animals were under sodium pentobarbital anesthesia was four times as great as the weights of organs removed with ether employed as the anesthetic, according to Hahn, Bale and Bonner.[425] In other studies, utilizing radioactive isotopes of iron, it was shown that when dogs were under sodium pentobarbital anesthesia as much as 30 per cent of the circulating red cell mass was contained within the engorged spleen.

Banti's Syndrome.—Limarzi and his associates [426] compared the findings in the sternal marrow of 21 patients with Banti's syndrome, 20 with portal cirrhosis, 5 with proved thrombosis of the splenic vein, 5 with idiopathic splenomegaly and 2 with Felty's syndrome, and 10 normal persons. The marrow from patients with Banti's disease revealed an increase in myeloid elements and megakaryocytes. The findings in other types of anemia and splenomegaly, including idiopathic splenomegaly, thrombosis of the splenic vein and Felty's syndrome, did not differ appreciably from those reported for Banti's syndrome. Splenectomy was performed on 4 of the patients with Banti's syndrome, and a reversal of the myeloid-erythroid ratio with marked immaturity of erythroid elements was noted prior to the operation in 3 instances. Two of the patients died shortly after the operation with evidence of hepatic disease, and the third failed to improve. In contrast, the fourth patient, with a normal myeloid-erythroid ratio and normal maturity of the red cell elements, was definitely improved after splenectomy. The authors feel that the findings in the marrow may be of prognostic significance and may serve as a guide in the selection of patients who are likely to benefit from removal of the spleen. An erythroblastic marrow with a reversal of the myeloid-erythroid ratio indicates a poor prognosis. When hyperplasia constitutes the only abnormality in the marrow, splenectomy may be helpful in correcting the abnormalities in the peripheral blood, and the operation may be beneficial in cases of "maturation arrest" of the myeloid elements. The authors suggest that a chronic toxic process may be an etiologic factor in Banti's syndrome. Splenectomy in cases of Felty's syndrome may give dramatic but transient improvement in the blood values, but death usually occurs within eighteen months. It is the opinion of Ravenna [427] that Banti's syndrome may occur independently of any obstruction of the portal circulation and that circulatory disturbances in the portal bed do not account for chronic, fibrous and congestive splenomegaly. Twelve cases were gathered from the necropsy protocols of the Michael Reese Hospital in which occlusion of the splenic or portal vein or both was not dependent on disease of the spleen but was caused by tumors in 11 cases and by a fibrous band in 1. The average weight of the spleens in these cases was 140 Gm., in contrast to the reported average weight of 1,000 Gm. in Banti's disease. Further support of the view that portal obstruction alone will not produce splenic enlargement is gained by the consistent failure to demonstrate splenomegaly experimentally in animals after complete, partial or intermittent obstruction of the splenic vein.

Eliason and Stevens [428] believe that splenectomy offers the patient with Banti's syndrome the best chance of survival. Their conclusion was based on 28 cases in which the spleen was removed. The mortality rate of the operation was 25 per cent, and the survival rate at 5 and 10 years was 28 and 21 per cent respectively. Figures collected from the literature showed that the ten year survival rate varied from 5 to 75 per cent in different series of cases.

Gaucher's Disease.—Sternal and splenic puncture aspirations in 2 cases of Gaucher's disease are reported in detail by Piaggio Blanco, Cerrutti and Paseyro.[429] In sternal marrow Gaucher cells totaled 1.2 and 0.4 per cent of the nucleated cells present, while they were found in much greater numbers in the material obtained by splenic puncture. A classification of Gaucher cells according to number and position of the nuclei is presented. Piaggio Blanco, Codebue and Paseyro [430] report the case of a 23 year old woman with advanced manifestations of Gaucher's disease, including rarefied bony lesions in the skull, who gave birth to a full term normal infant.

425. Hahn, P. F.; Bale, W. F., and Bonner, J. F., Jr.: Removal of Red Cells from the Active Circulation by Sodium Pentobarbital, Am. J. Physiol. **138**: 415, 1943.

426. Limarzi, L. R.; Jones, R. M.; Paul, J. T., and Poncher, H. G.: Sternal Marrow in Banti's Syndrome and Other Splenomegalic States: The Effect of Splenectomy, Am. J. Clin. Path. **13**:231, 1943.

427. Ravenna, P.: Splenoportal Venous Obstruction Without Splenomegaly: Further Contribution to the Pathogenesis of Fibrocongestive Splenomegaly (Banti's Syndrome), Arch. Int. Med. **72**:786 (Dec.) 1943.

428. Eliason, E. L., and Stevens, L. W.: Surgery of Spleen in Blood Dyscrasias, Surgery **13**:177, 1943.

429. Piaggio Blanco, R. A.; Cerrutti, N., and Paseyro, P.: Enfermedad de Gaucher familiar, Arch. urug. de med., cir. y especialid. **21**:245, 1942.

430. Piaggio Blanco, R. A.; Codebue, J. L., and Paseyro, P.: Enfermedad de Gaucher y embarazo, con lesiones óseas craneanas, Arch. urug. de med., cir. y especialid. **21**:257, 1942.

Petit and Schleicher [431] observed a 79 year old Jewish man with several unusual features of this disease. A severe anemia led to sternal aspiration, which revealed foam cells of the Gaucher type. The spleen was normal in size, and roentgen examination of the bones failed to demonstrate any skeletal defect. At necropsy no gross abnormalities were evident, but on microscopic examination Gaucher cells were found involving the marrow of the femur, tibia, ribs and sternum.

A 6 year old white child with primary xanthomatosis of the spleen with splenomegaly and anemia was studied by Dreyfuss and Fishberg.[432] Histologic and quantitative chemical analysis of the spleen removed at operation revealed that lecithin, cephalin and total cholesterol were the chief lipids present. General clinical improvement followed splenectomy, and other evidence suggested that the disease process was localized to the spleen.

HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

General Observations.—An outstanding monograph on the physiology of hemostasis and the hemorrhagic diseases has been published by Quick.[433] The author's own investigations regarding prothrombin and methods for its detection, the hypoprothrombinemia of avitaminosis K, the preparation and use of heparin and the action of the hemorrhagic agent dicoumarin are widely recognized and assure an authoritative background for the book. Chapters are devoted to the discussion of thrombin, prothrombin, fibrinogen, thromboplastin, platelets and the anticoagulants. Many isolated bits of information dealing with these confused subjects are assembled and clarified. Each topic is introduced by a concise historic review, and an unusually complete list of references to the original work is given at the end of each chapter. Chapters on the hemorrhagic diseases are followed by sections devoted to vitamin K deficiencies, the bleeding disease of the newborn and the toxic sweet clover disease. An appendix in which he outlines the technical methods of proved value in the study of hemorrhagic problems forms the concluding section of the book. The work reflects the author's extensive laboratory and investigative experience. It will be of particular value to clinicians who deal at first hand with patients with defective hemostasis and will serve as a source of basic information concerning the mechanisms involved.

Kato [434] presents a lengthy review of the hemorrhagic states encountered in pediatric practice particularly. Kugelmass [435] reviews the hemorrhagic problems of children that are of especial interest to surgeons.

Spontaneous hemorrhages associated with chronic nephritis are generally recognized clinically without difficulty but sometimes present diagnostic problems. Behr [436] reports the case of a 21 year old man who had had weakness, epistaxes and anemia of two months' duration. The platelet count was 192,000 per cubic millimeter. Routine urinalyses gave normal results. The anemia required several blood transfusions, but there was little improvement and the patient died of nasal and rectal hemorrhages with the diagnosis not certainly established. At autopsy small sclerotic kidneys with adherent capsules were found. The microscopic appearance was that of chronic glomerulonephritis.

Shafiroff and associates [437] studied experimentally the effect of hemorrhage on the coagulability of blood and lymph in dogs. The coagulation time, plasma coagulation time, prothrombin time, antithrombin time and fibrinogen concentration were determined in parallel for both blood and lymph during the experiments. Progressive rapid bleeding rendered both blood and lymph of normal animals hypercoagulable. The coagulation time of animals whose blood had previously been rendered hypocoagulable by administration of protamine, peptone or heparin was likewise reduced. This increased coagulability following hemorrhage or bleeding was shown to result from increased mobilization of thromboplastin. The lymph of animals given injection of protamine and peptone remained hypocoagulable, however, in spite of the loss of blood.

Purpura.—Evans and Perry [438] report a clinical study of the cases of 75 patients with essential thrombopenic purpura cared for at the London Hospital between 1927 and 1938. The patients were followed until the outbreak of the war, and

431. Petit, J. V., and Schleicher, E. M.: Atypical Gaucher's Disease, Am. J. Clin. Path. **13**:260, 1943.

432. Dreyfuss, M. L., and Fishberg, G. H.: Localized Agnogenic (of Unknown Origin) Xanthomatosis of Spleen with Splenomegaly and Anemia, Am. J. M. Sc. **206**:458, 1943.

433. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

434. Kato, K.: Hemorrhagic States of Infants and Children, Clinics **2**:33, 1943.

435. Kugelmass, I. N.: Hemorrhagic Problems in Child Surgery, J. Internat. Coll. Surgeons **6**:133, 1943.

436. Behr, G.: Spontaneous Haemorrhages in Chronic Nephritis, Lancet **1**:238, 1943.

437. Shafiroff, B. G. P.; Doubilet, H.; Siffert, R., and CoTui: The Effect of Hemorrhage on Normal and Hypocoagulable Blood and Lymph, Am. J. Physiol. **138**:753, 1943.

438. Evans, H., and Perry, K. M. A.: Thrombocytopenic Purpura, Lancet **2**:410, 1943.

12 of them until July 1942. Before puberty the patients were evenly divided as to sex, but after that age there was a preponderance of 5 females to 1 male. Of the 30 patients under 15 years of age, 5 died during the period of observation. The causes of death were subdural hemorrhage in 3 cases and severe hemoptysis and septic meningitis following chronic meningitis in 1 case each. The purpura persisted in 4 patients in spite of splenectomy and in 2 in whom the spleen was not removed. Ten recovered without splenectomy and 5 with splenectomy. Thirty-eight of the 75 patients over 15 years of age were females. Menorrhagia was a constant and severe added symptom in this group. Thyrotoxicosis was associated with the purpura in 4 cases. One of the women with purpura became pregnant; the symptoms of purpura gradually cleared, with the platelet count rising to 770,000 and the bleeding time falling to two and one-half minutes. In 2 patients leukocytosis with a greatly increased percentage of lymphocytes was present. The authors discuss the relationship of endocrine factors, pregnancy, and aplastic and refractory anemias to thrombopenic purpura. Transfusions of fresh blood appeared to be the only medical treatment of value. Splenectomy was curative in 7 of 7 males and in 7 of 17 females. There were 3 operative deaths. The authors consider splenectomy a life-saving measure advisable in desperate cases in spite of the high risk.

A general review of the subject of purpura is presented by Ceballos.[439] Phythyon and Lartz [440] report another instance of pregnancy complicated in the seventh month by the appearance of thrombopenic purpura. Blood transfusions were of only temporary benefit, and surgical removal of the spleen was undertaken. After splenectomy the platelet count returned to normal but the pregnancy terminated four days postoperatively in a stillborn child. Aguilar Giraldes [441] reports 3 cases of purpura occurring early in infancy. Ayerza and his associates [442] report a case of abdominal purpura of Henoch's type.

A number of case reports of thrombopenic purpura associated with lymphocytosis have appeared during the past year. Duncan [443] reports such a condition in a 4 year old girl. The illness was of acute onset, with abdominal rigidity and a temperature reaching 104 F. The white cell count rose to a high level of 110,000, and the platelet count fell as low as 90,000. The white cells were predominantly small lymphocytes and were neither atypical nor immature in appearance. The patient recovered in five weeks. Tasker [444] reports the case of a 51 year old woman in whom thrombopenic purpura and lymphocytosis developed. His patient had had unusual epistaxes for one year, ease of bruising for two weeks and persistent bleeding from the nose and uterus for six days. Generalized petechial hemorrhages and enlargement of lymph nodes were present. Neither the liver nor the spleen was palpable. The leukocytes numbered 13,720 per cubic millimeter, with 13.5 per cent large and 69 per cent small lymphocytes. The platelet count was 18,650. The sternal marrow appeared normal. In spite of blood transfusions bleeding continued, and on the twenty-third day of the patient's hospitalization the spleen was removed. The platelets increased to normal levels, and there was clinical improvement. The enlarged lymph nodes persisted for eight and a half weeks.

Morlock and Hall [445] discuss the hemorrhagic tendencies of patients with hepatic disease which may ensue despite administration of vitamin K. Their interest was aroused by a jaundiced patient with chronic disease of the biliary tract who was prepared for operation by parenteral injections of synthetic vitamin K and other usual measures. At the outset of the operation, despite a nearly normal prothrombin level, profuse bleeding impossible to control by the customary procedures was encountered in the abdominal wall and the operation had to be discontinued. Subsequent investigation revealed a reduction in the platelets to 56,000 to 68,000. Eighty cases of cirrhosis were reviewed as to the possible relation between thrombopenia and bleeding tendencies, and of the 47 patients in whom a bleeding tendency was found 25.5 per cent had had definite thrombopenia. Only 6.6 per cent of the group without evidence of bleeding had thrombopenia. Fifty cases of so-called splenic anemia with associated hepatic disease were reviewed from the same standpoint, and of 39 patients with abnormal bleeding 19 had definite thrombopenia. The cause of the thrombopenia occurring with disease of the liver remains obscure.

439. Ceballos, A.: Púrpura, Prensa méd. argent. **30**:1086, 1943.

440. Phythyon, D., and Lartz, R. E.: Thrombocytopenic Purpura, Am. J. Obst. & Gynec. **45**:715, 1943.

441. Aguilar Giraldes, D.: Sobre 3 casos de sindromes purpuricos en niños de primera infancia, Arch. argent. de pediat. **18**:493, 1942.

442. Ayerza, L.; Taboada, F., and Nino, S.: Púrpura abdominal de Henoch, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:211, 1943.

443. Duncan, P. A.: Acute Infectious Lymphocytosis, Am. J. Dis. Child. **66**:267 (Sept.) 1943.

444. Tasker, J. R.: Thrombocytopenic Purpura with Lymphocytosis, Proc. Roy. Soc. Med. **36**:355, 1943.

445. Morlock, C. G., and Hall, B. E.: Association of Cirrhosis, Thrombopenia and Hemorrhagic Tendency, Arch. Int. Med. **72**:69 (July) 1943.

Tager and Klinghoffer [446] report the case of a 20 year old female student in whom acute thrombopenic purpura hemorrhagica developed, with a large number of abnormal lymphocytes present in the peripheral blood. The provisional diagnosis, agreed on by many hematologists who studied the blood films, was acute leukemia. The illness began with slight gingival bleeding, a few purpuric spots and a feeling of chilliness. When the patient was admitted to the hospital twenty-four hours later the petechiae were more numerous and a slight fever was present but neither the spleen nor lymph nodes were enlarged. Gross hematuria and bloody stools appeared later. Prolonged bleeding and clotting time, absence of clot retraction and a positive reaction to the tourniquet test were present. The leukocytes were increased to over 14,000 initially, and on one occasion 68 per cent of the cells were pathologic lymphocytes. Clinical improvement was rapid after the first week. The chief therapy was a series of small transfusions. The platelet count returned to normal in four weeks' time, but pathologic cells could be found in the blood for as long as seventy days after the onset of the illness. The patient was followed for two and a half years and remained well.

Gerstenberg and Reinwein [447] emphasized the frequency with which thrombopenic purpura may be symptomatic of some underlying disorder, such as leukemia, agranulocytosis, aplastic anemia, hemolytic icterus, metastatic carcinoma to the bone marrow, or chemical or medicinal poisoning. They report the case of a patient with thrombopenic purpura whose spleen was removed and found to be tuberculous. They collected and reviewed a number of similar cases from the literature. Davis [448] reports observing 500 cases of different types of purpura personally. In 63 per cent of the cases the purpura occurred symptomatically in some other disease. Flor Jorganes [449] presents a case report of a young adult with Schönlein's purpura. There were recurrent pain and edema about the joints, cutaneous purpura, fever and a pulmonary infiltration possibly of tuberculous origin.

Stein and Miller [450] report a study of the blood in the tropical disease onyalai, which occurs in Africa from the equator south as far as Johannesburg. One of the striking clinical features of the disease is the presence of many "blood blisters," or hemorrhagic bullae, about the mouth, tongue and palate. It is a serious disease, with an average mortality of about 22.5 per cent. The patients were found to have profound thrombopenia, prolonged bleeding time, normal coagulation time, poor clot retraction and decreased capillary resistance. The cause of the disease was not proved, but it appeared to be a form of idiopathic thrombopenic purpura, possibly of infectious origin. In the treatment of the disease, symptomatic measures, sulfonamide compounds and blood transfusions were used.

Banks and McCartney,[451] in considering the clinical syndromes associated with meningococcemia, have unearthed several more case reports which appeared as early as 1894 of fulminating illnesses associated with massive petechial eruptions and bilateral adrenal hemorrhages, probable examples of what in recent years has come to be designated the Waterhouse-Friderichsen syndrome. They report 11 new cases of meningococcic adrenal disease; 8 of the patients died and the diagnosis was proved at autopsy, while the other 3 recovered. Meningococci were isolated from 6 of the patients who died and from 2 of those who survived. The fulminating septicemia of sudden onset with a petechial and massive purpuric rash, cyanosis, grayish pallor, vomiting, diarrhea, dehydration, thready or imperceptible pulse, extremely low blood pressure and muscular flaccidity were the usual clinical features. Signs of meningitis often appeared later.

The authors submit clinical and pathologic evidence that two syndromes may occur in meningococcic adrenal disease. In one, the adrenal syndrome, the main organic lesion is confined to the adrenal glands. Some patients with this type may recover, since the pathologic lesion may be only thrombotic necrosis or gross edema with focal areas of inflammatory adrenalitis. The mental condition remains clear, even to the end in fatal cases. In the second type, or mixed adrenal-encephalitic syndrome, lesions both in the brain tissue and in the adrenal glands occur. Coma is present, and breathing is rapid and stertorous or terminally of Cheyne-Stokes type

446. Tager, M., and Klinghoffer, K. A.: Acute Thrombocytopenic Purpura Hemorrhagica with Lymphocytosis: Report of a Case, Ann. Int. Med. **18**:96, 1943.

447. Gerstenberg, W. H., and Reinwein H.: Symptomatische thrombopenische Purpura bei Milztuberkulose, Beitr. z. Klin. d. Tuberk. **95**:517, 1940.

448. Davis, E.: Purpura of the Skin: A Review of Five Hundred Cases, Lancet **2**:160, 1943.

449. Flor Jorganes, J.: Purpura de Schönlein-Henoch, Medica, Matanzas **2**:34, 1943.

450. Stein, H. H., and Miller, E.: Acute Thrombocytopenic Purpura Associated with Haemorrhagic Bullae, with Special Reference to Onyalai, South African J. M. Sc. **8**:1, 1943.

451. Banks, H. S., and McCartney, J. E.: Meningococcal Adrenal Syndromes and Lesions, Lancet **1**:771, 1943.

without abnormal thoracic signs. No patients with this type survived. In all cases the therapy should include immediate and vigorous administration of a sulfonamide compound, intravenous injection of solutions of sodium chloride and dextrose, and administration of adrenal cortical extract or desoxycorticosterone acetate, together with treatment for shock.

Several other case reports of this syndrome have appeared. Taylor and Kean [452] report 2 fatal cases in infants 25 days and 2 months old respectively. Although meningococci were not isolated in either case, the clinical syndrome was typical, with death following a short, fulminating illness. Blotchy cyanosis and edema were present clinically, and necropsy showed massive adrenal hemorrhages in both cases. Gordon and Shimkin [453] report a case of fatal meningococcemia in a young physician. Malaise and headache followed by fever began twenty hours before his hospitalization. The white blood cell count on the patient's admission to the hospital was 26,000. Extensive petechiae appeared the following day, and administration of sulfadiazine was started. Circulatory collapse ensued in a few hours. In spite of treatment with sulfadiazine, meningococcus antitoxin, transfusions of blood and plasma, adrenal cortex extract and supportive measures, he died ninety hours after the onset of his illness. Cultures of both blood and spinal fluid yielded Neisseria intracellularis. Autopsy showed purulent meningitis, bronchopneumonia, focal necrosis of the pituitary gland and focal hemorrhages in the brain, meninges, lungs, adrenal glands and renal pelves.

Leichliter and Fish [454] report a case of fatal meningococcemia in a soldier. After two weeks of symptoms referable to the upper respiratory tract and cough there was an acute appearance of fever and chills. Therapy with a sulfonamide compound was instituted early, but death occurred in spite of the treatment. A blood culture yielded meningococci. Necropsy revealed acute meningococcic meningitis, massive hemorrhage into the adrenals and bronchopneumonia. Rucks and Hobson [455] review the clinical and bacteriologic aspects of the disease and report a case of its occurrence in a 3 year old child. The onset was acute, with nausea and vomiting followed by a rise of temperature to 106 F. and a chill. A hemorrhagic rash, stupor and shock appeared within eight hours of the first symptom. Treatment with sodium sulfathiazole, adrenal cortex extract and other measures resulted in recovery after a stormy course. Blood cultures were negative except for one finding of Staphylococcus aureus believed to be a contaminant.

Cuningham [456] reports 4 cases of the meningococcemic syndrome in children 4 weeks to 2½ years old. The onset in all cases was abrupt, with irritability, anorexia and fever. Cyanosis, petechiae and confluent hemorrhages appeared later. Only 1 patient showed signs of meningitis. All 4 patients died between ten and a half and twenty-six hours after the onset of symptoms. Meningococci were cultured from the blood post mortem in every case. Pathologic examination showed gross adrenal hemorrhage and necrosis in but 2 of the cases. The organs showed general edema, severe toxic changes and congestion. McNamara [457] reports 5 cases of purpura associated with acute infections. Two of his patients died; these presented typical examples of the Waterhouse-Friderichsen syndrome. One patient recovered with sulfapyridine therapy, and 2 recovered without specific treatment.

Thrombopenic purpura occurring as a toxic reaction following administration of sulfonamide drugs has been reported in several additional cases during the past year. Gorham and his colleagues [458] review 5 cases previously reported and present 3 new cases. In the combined series fatal purpura was caused by sulfanilamide, sulfapyridine and sulfadiazine. One patient was given azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) as well as sulfanilamide, and the 1 patient with purpura following the use of sulfathiazole recovered. In 2 and possibly 3 of the fatal cases the drug was continued in use for twenty-four to forty-eight hours after petechial hemorrhages or bleeding appeared. In the 4 cases in which the patients recovered, administration of the drug was stopped on the

452. Taylor, C. E., and Kean, B. H.: Waterhouse-Friderichsen Syndrome on Isthmus of Panama, Am. J. Dis. Child. **65**:426 (March) 1943.

453. Gordon, W. H., and Shimkin, M. B.: Fulminating Meningococcemia with Purpura, Meningitis and Focal Necrosis of Pituitary, J. A. M. A. **123**:147 (Sept. 18) 1943.

454. Leichliter, J. W., and Fish, C. E.: The Waterhouse-Friderichsen Syndrome: A Report of a Case in a Soldier, Mil. Surgeon **93**:77, 1943.

455. Rucks, W. L., and Hobson, J. J.: Purpura Fulminans (Waterhouse-Friderichsen Syndrome): Report of a Case with Recovery, J. Pediat. **22**:226, 1943.

456. Cuningham, J. A. K.: Adrenal Hemorrhage in Meningococcal Septicemia, New Zealand M. J. **41**:238, 1942.

457. McNamara, K. N.: Acute Septicemic Purpura, New Zealand M. J. **42**:51, 1943.

458. Gorham, L. W.; Propp, S.; Schwind, J. L., and Climenko, D. R.: Thrombocytopenic Purpura Caused by Sulfonamide Drugs: A Report of Three Cases, Am. J. M. Sc. **205**:246, 1943.

first appearance of hemorrhagic manifestations. Since thrombopenia precedes the appearance of purpura, the number of platelets in the blood film should be routinely checked along with possible granulocytopenia in guarding against toxic reactions, and this certainly should not be omitted if petechiae or hemorrhage appears. Thrombopenic purpura developed after as little as 5.5 Gm. of sulfathiazole had been given in three days, and death occurred after as little as 7 Gm. of sulfanilamide had been given in four days. Half of the patients in whom thrombopenic purpura developed as a result of treatment with sulfonamide compounds died.

Hurd and Jacox [459] report 2 cases of this toxic reaction to sulfonamide compounds, 1 case terminating fatally after sulfadiazine was used in the treatment of pneumonia. In their second case an oozing epistaxis appeared after 12 Gm. of sulfathiazole had been given in the treatment of pneumococcic pneumonia. A petechial rash appeared soon afterward, and two bloody stools were passed. The pneumonia was successfully treated with antipneumococcus rabbit serum. Later during convalescence tests for sensitivity to sulfathiazole were made. Scratch, patch and intradermal tests gave negative results. Sulfathiazole in doses of 0.1 and 0.25 Gm. given orally did not affect the platelet count. When three doses of 1.5 Gm. each were given at four hour intervals there was a definite decrease in the platelets in the films of peripheral blood, the bleeding time increased to eight minutes and the reaction to the Rumpel-Leede test became positive. Two weeks later a similar experiment gave the same result, the platelet count falling from 190,000 to 35,000, after which there was a slow rise over a period of about four days. A similar test was made with sulfadiazine, which apparently had never been given to the patient before. After 8 Gm. had been administered in twenty-four hours the platelet count again fell and the Rumpel-Leede test gave a positive reaction. The effect of sulfadiazine was less pronounced and less prolonged than that of sulfathiazole in this case.

Kracke and Townsend [460] report in detail 2 cases of thrombopenic purpura following sulfathiazole therapy and mention having observed 3 similar cases. In 1 case gastrointestinal bleeding began twenty-four hours after the first dose of sulfathiazole. Although only 16 Gm. was given in three days, the use of the drug was not discontinued until the second day after the onset of hemorrhagic symptoms, at which time sulfapyridine was substituted. The patient died. In the second case about 10 Gm. of sulfathiazole were given in two days for a sore throat. Nausea, vomiting and hematuria appeared on the third day and purpuric spots, uterine bleeding and bloody sputum on the sixth day. The patient finally died of renal failure. To observe the effect of sulfathiazole on the blood platelets in a larger series of persons the authors performed serial platelet counts for 61 patients receiving sulfathiazole. They found that early in the treatment the platelet count tends to be depressed but after cessation of therapy it often increases above normal.

Losada and Fernandez [461] report having seen 3 patients with purpura due to sulfonamide compounds (in 1 of them it followed the administration of sulfaguanidine) and present 1 case report in detail. Lehmann [462] observed a patient who was given 3 Gm. of sulfadiazine daily for three days, after which extensive purpura appeared over the lower extremities. The platelet count was depressed to 92,000. After the use of the drug was discontinued the purpura cleared and the patient recovered. Williams [463] noted purpura in a soldier as a part of a general toxic reaction to sulfapyridine. A cutaneous rash and edema were also present. Several courses of the drug had been given over a month's time in the treatment of gonorrhea. Sutliff and his colleagues [464] studied toxicity of sulfonamide compounds as a cause of death in the city of New York during the year 1941. They found that 2 of the 28 fatal reactions were due to purpura. Cecil in discussing this paper mentions 2 additional cases which he observed personally.

Hemophilia.—A general review of the recent developments in the study of hemophilia is presented by Kark.[465] In regard to the major problem of delayed blood coagulation, it is now established that there is no abnormality in fibrin-

459. Hurd, R. W., and Jacox, R. F.: Thrombopenic Purpura Developing as a Complication of Sulfathiazole and Sulfadiazine Therapy, J. A. M. A. **122**:296 (May 29) 1943.

460. Kracke, R. R., and Townsend, E. W.: The Effect of Sulfonamide Drugs on the Blood Platelets: Report of Two Cases of Thrombopenic Purpura and Experimental Studies on Patients Receiving Sulfonamide Drugs, J. A. M. A. **122**:168 (May 15) 1943.

461. Losada, L. M., and Fernandez, W. S.: Purpura trombopénico por sulfanilamida, Rev. méd. de Chile **70**: 524, 1942.

462. Lehmann, J. H.: Acute Thrombocytopenic Purpura, Northwest. Med. **42**:325, 1943.

463. Williams, H. V.: Hepatosplenomegaly with Other Clinical Reactions to Sulphapyridine, Lancet **1**: 105, 1943.

464. Sutliff, W. D.; Helpern, M.; Griffin, G., and Brown, H.: Sulfonamide Toxicity as a Cause of Death in New York City in 1941, J. A. M. A. **121**: 307 (Jan. 30) 1943.

465. Kark, R.: Recent Developments in Hemophilia, Clinics **2**:15, 1943.

ogen, thrombin, calcium or prothrombin. The essential factor in the disorder lies in defective thromboplastic activity. At least three explanations are offered for this abnormality by different groups of investigators. The decreased tendency for agglutination and lysis of platelets which occurs in hemophilia may lead to a slow rate of thromboplastic liberation and thus a delay in blood coagulation (for discussion see Quick [433]). A second mechanism leading to the same result implicates increased antithromboplastic activity in hemophilia (see next paragraph). Kark, however, accepts the view that the important cause of the delay in coagulation lies in a diminished amount of plasma thromboplastin. It was earlier demonstrated (Lozner, Kark and Taylor [466]) that fresh, citrated normal plasma rendered free of cells, fibrinogen and prothrombin when injected into patients with hemophilia causes a reduction in blood coagulation time. The work supporting the concept of Nolf that cell-free plasma contains all the elements necessary to form a clot is reviewed, as well as the experiments identifying the "globulin substance" of Taylor, or "plasma thromboplastin," as an element specifically deficient in hemophilia.

The coagulation defect in hemophilia has been further investigated by Tagnon, Davidson and Taylor.[467] These investigators previously demonstrated the presence of a proteolytic enzyme in normal, cell-free human plasma treated with chloroform. This enzyme was associated with the globulin fraction of the plasma proteins, and it could also be prepared by the action of chloroform on a saline solution of human plasma euglobulin. Since hemophilic blood was known to have a defective coagulation activity associated with plasma euglobulin, hemophilic and normal human plasmas were compared as sources of the enzyme activity. It was observed that the rate of dissolution of the clot obtained by the action of chloroform was much slower with hemophilic plasma than with normal human plasma. Fibrinogenolysis was also much more rapid with preparations of normal plasma than of hemophilic plasma. It was concluded that the proteolytic activity of chloroform preparations of hemophilic plasma is significantly less than for such preparations of normal plasma. Further studies are necessary before one can conclude that the parenteral activity of "globulin substance" in hemophilia is due to this enzyme alone.

Tocantins [468] reported experiments showing that both normal and hemophilic blood plasma, collected with special precautions, when incubated with dilute extracts of homologous brain tissue reduces the clot-accelerating action of these extracts. This activity is attributed to plasma antithromboplastin. He found that the substance is exhausted during the stage preceding the inception of clotting, that it has a certain degree of species specificity and that it is made ineffective by dilution, by heating to 65 C. for five minutes, by exposure to tissue juices and by standing in contact with red blood cells. Hemophilic plasma was found to have an antithromboplastic activity five to eight times greater than normal plasma. The author suggests that this substance, by reducing the amount of available free thromboplastin released from blood or tissue cells, delays the activation of prothrombin and thereby plays an important role in maintaining the fluidity of circulating blood and in postponing the inception of clotting in shed blood. In hemophilia the delayed coagulation time may be due to the presence of excess antithromboplastin, so that more free thromboplastin is required and a longer time elapses before neutralization allows coagulation to proceed.

The most effective therapy for hemophiliac bleeding is transfusion of normal blood or plasma. A patient who showed the possible detrimental effect of frequent transfusions was observed by Munro and Jones.[469] He was a 36 year old hemophiliac who in a period of about four years had received some 3,000 cc. of whole blood and 5,000 cc. of plasma for prophylactic reasons. During the latter part of this period of frequent transfusions the coagulation time tended to become progressively longer and the beneficial effect of each transfusion less. In vitro experiments of considerable interest showed that during the period of transfusion therapy plasma from the hemophiliac caused a progressive prolongation of the coagulation time of normal plasma after recalcification. It was suggested that this effect may be due to the antithromboplastin demonstrated by Tocantins. If so, transfusions are of value in cases of hemophilia in temporarily neutralizing this substance in the circulating blood, but after repeated transfusions the antithromboplastin may return to

466. Lozner, E. L.; Kark, R., and Taylor, F. H. L.: Coagulation Defect in Hemophilia: Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin, J. Clin. Investigation **18**:603, 1939.

467. Tagnon, H. J.; Davidson, C. S., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia: A Comparison of the Proteolytic Activity of Chloroform Preparations of Hemophilic and Normal Human Plasma, J. Clin. Investigation **22**:127, 1943.

468. Tocantins, L. M.: Demonstration of Antithromboplastic Activity in Normal and Hemophilic Plasmas, Am. J. Physiol. **139**:265, 1943.

469. Munro, F. L., and Jones, H. W.: The Detrimental Effect of Frequent Transfusions in the Treatment of a Patient with Hemophilia, Am. J. M. Sc. **206**:710, 1943.

levels even higher than the original. The authors believe that injections of blood and plasma in the treatment of hemophilia should be reserved for emergency use.

McDonald and Lozner [470] present a study of the roentgen findings in hemophilic arthritis, including the acute hemarthroses and the chronic degenerative type of disease of the joints which follows repeated hemorrhages. After acute hemarthroses joints were observed to return to normal roentgenologically. With recurrent hemorrhages leading to chronic arthritic changes there was a progressive advance in the roentgen signs. The most characteristic bony changes were areas of subarticular cystic absorption 1 to 10 mm. in diameter. The various joints were involved in the following order of frequency: knees, elbows, ankles, and wrists. Echternacht [471] reports a huge osseous hematoma in a 13 year old hemophiliac which followed an injury to the tibia. There was roentgen evidence of destruction of bone and of thickening and elevation of the periosteum. The roentgen appearance could not be differentiated from that of a rapidly progressive bone sarcoma. A similar condition in the large toe was described in a case record of the Massachusetts General Hospital.[472] Mark [473] and Baer and his associates [474] report 2 rare instances of intracranial hemorrhage in patients with hemophilia, 1 having an intracerebral hemorrhage and the other a fatal subdural hematoma. Freedman and his colleagues [475] report nontraumatic hemothorax complicating hemophilia. An unusual complication of hemorrhage is reported by Baird and Fox [476] in a 4½ year old boy with hemophilia. During the course of an infection of the upper respiratory tract massive sublingual and paratracheal hemorrhage occurred, resulting in acute respiratory embarrassment. A tracheotomy was done with immediate symptomatic relief. The patient recovered.

470. McDonald, E. J., and Lozner, E. L.: Hemophilic Arthritis, Am. J. Roentgenol. **49**:405, 1943.

471. Echternacht, A. P.: Pseudotumor of Bone in Hemophilia, Radiology **41**:565, 1943.

472. Hemophilic Hemarthrosis, Cabot Case 29251, New England J. Med. **228**:831, 1943.

473. Mark, P. F.: Cerebral Hemorrhage in Hemophilia: Case Report with Necropsy Findings, Yale J. Biol. & Med. **15**:185, 1942.

474. Baer, S.; Goldburgh, H. L., and Pearlstine, B.: Recurrent Intracranial Hemorrhages in a Patient with Hemophilia, J. A. M. A. **121**:933 (March 20) 1943.

475. Freedman, P.; Levine, S., and Solis-Cohen, L.: Hemothorax in Blood Dyscrasias, Am. J. M. Sc. **205**: 692, 1943.

476. Baird, K. H., and Fox, M. S.: Severe Sublingual and Paratracheal Hemorrhage in Hemophilia with Recovery Following Tracheotomy, J. Pediat. **23**: 90, 1943.

Hereditary Hemorrhagic Telangiectasia.—Figi and Watkins [477] report on 20 patients with hereditary hemorrhagic telangiectasia seen in the Section on Otolaryngology of the Mayo Clinic. The commonest symptom of this disease is epistaxis, and the most frequent location of the telangiectasia is on the nasal septum. Other sites in order of frequency include the tongue, face, lips and cheeks. The nasal telangiectases are located on both sides of the cartilaginous septum, where they are readily traumatized. The loss of blood may vary from an ooze to a massive hemorrhage, and severe degrees of anemia may result. In the treatment of active bleeding local pressure exerted by an inflated finger cot is the most effective procedure. For more lasting benefit electrocoagulation done under local anesthesia is regarded as the best therapy. However, this procedure is difficult and tedious and often requires repetition as new nevi develop. Pangaro and Iacovone [478] present the case record of a 36 year old man with hereditary hemorrhagic telangiectasia in whom a severe anemia developed due to frequent nosebleeds recurring over a period of nine years. His liver and spleen were enlarged, possibly, it was thought, because of visceral telangiectasia. Lipscomb [479] reports briefly on a brother and a sister both of whom had elliptic red blood cells and telangiectasia. There was a history of splenomegaly and jaundice in their cases.

Prothrombin and Vitamin K.—Nature of Prothrombin: Quick [480] reports important advances in the study of the nature of prothrombin. He observed that in stored oxalated human plasma unless oxygen was excluded the quantity of prothrombin progressively decreased in a matter of days to very low levels. A plasma low in prothrombin was likewise produced by the administration of dicoumarin. Mixing equal parts of these plasmas, both deficient in prothrombin, resulted in a normal prothrombin level for the combined plasma. Previous experiments with the quantitative removal of calcium from the blood as related to prevention of coagulation had led to the conclusion that calcium was bound to the prothrombin molecule itself and that on the addition of decalcifying agents this calcium was torn from the prothrombin, the latter being

477. Figi, F. A., and Watkins, C. H.: Hereditary Hemorrhagic Telangiectasia, Ann. Otol., Rhin. & Laryng. **52**:330, 1943.

478. Pangaro, J. A., and Iacovone, R. C.: Enfermedad de Rendu-Osler de forma hepatosplenomegálica, Semana méd. **1**:659, 1943.

479. Lipscomb, J. M.: Elliptocytosis Associated with Hereditary Hemorrhagic Telangiectasia, Proc. Roy. Soc. Med. **36**:357, 1943.

480. Quick, A. J.: On the Constitution of Prothrombin, Am. J. Physiol. **140**:212, 1943.

left in an inactive state. With the new data it appeared most likely that prothrombin was composed of two separate and essential factors combined with calcium. The two components, designated A and B, when bound together by calcium form a stable compound protected against external factors such as oxidation.

Component A of prothrombin, labile in vitro and disappearing during storage, was easily destroyed by heating to 60 C. for five minutes. While it was stable in its native or unmodified state as a part of the prothrombin complex, rapid oxidation occurred in citrated or oxalated plasma. In the plasma of the animal treated with dicoumarin this component was found to be quantitatively unaltered.

Plasma treated with aluminum hydroxide has previously been considered free of prothrombin. Quick found, however, that only component B was adsorbed in this procedure and that component A was left quantitatively behind. Preliminary studies showed that vitamin K deficiency, like administration of dicoumarin, produced reduction in only the B component of prothrombin. No instance of hypoprothrombinemia due to a reduction in the A component has as yet been encountered clinically.

The effect of storage at various temperatures on the prothrombin clotting time of human plasma was investigated by Page and de Beer.[481]

The prothrombin time increased directly with the storage time and with the storage temperature. Brambel and Loker [482] report an investigation of Quick's prothrombin method as applied to dilute plasma. They recommend this modification both for reliability and for increased sensitivity. By this method a normal acceleration of clotting time was found in phlebitis, in postoperative surgical trauma and during childbirth.

Macfarlane and his associates [483] reviewed the evidence indicating that the conversion of prothrombin to thrombin is accelerated by various fatty substances. Lecithin, plasma fat or even cream fat was found to be active in this regard. A fatty substance of some type appears to be necessary in the process of blood coagulation. Maltaner and Maltaner [484] compared the role of cephalin with that of thromboplastin in the coagulation of vitamin K–deficient chick plasma and dioxalated horse plasma. The action of the two substances was found to be entirely different.

Idiopathic Hypoprothrombinemia.—According to Giordano,[485] his case of idiopathic hypoprothrombinemia is the third reported in the literature and the first of proved familial incidence. His patient was a 22 year old Polish man who had required several hospitalizations and blood transfusions for uncontrolled nosebleeds, hemorrhages following extractions of teeth and posttraumatic hemorrhages into the soft tissues. Examination of his blood showed moderately severe anemia, a positive reaction to the tourniquet test and normal bleeding, clotting and clot retraction time. Administration of vitamin K was of no benefit, while transfusions of plasma only temporarily elevated the lowered prothrombin, which ranged under 10 per cent of normal. The patient's serum mixed with equal parts of normal plasma or serum resulted in a normal prothrombin time. It was thought that one of the prothrombin components described by Quick might be defective or lacking.

A similar bleeding tendency in the patient's sister had required several admissions to the hospital, a hysterectomy and a splenectomy. Her prothrombin level was 24 per cent of normal. Both parents and a brother had lower than normal levels also. A positive reaction to the tourniquet test was present in all, and except for a slightly low serum protein content no other abnormalities of the blood were discovered in the family.

Therapeutic Use of Vitamin K.—Warner [486] and Dam [487] present concise articles on the medical aspects of vitamin K deficiency. According to Dam the daily requirement for adults is not known but pure alimentary vitamin K deficiency is rare. Food deprivation, severe chronic diarrhea or perhaps depression of the intestinal flora by treatment with sulfonamide compounds might lead to a deficiency.

Allen [488] reported a study of the therapeutic safety of a water-soluble synthetic vitamin K preparation, which was given to 48 patients with prothrombin deficiencies. In 31 cases the low

481. Page, R. C., and de Beer, E. J.: The Effect of Storage at Various Temperatures on the Prothrombin Clotting Time of Human Plasma, Am. J. M. Sc. **205**: 257, 1943.

482. Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, Proc. Soc. Exper. Biol. & Med. **53**:218, 1943.

483. Macfarlane, R. G.; Trevan, J. W., and Attwood, A. M. P.: Participation of a Fat Soluble Substance in Coagulation of the Blood, J. Physiol. **99**:7P, 1941.

484. Maltaner, F., and Maltaner, E.: The Role of Cephalin and "Thromboplastin" in the Coagulation of Vitamin-K-Deficient Chick Plasma, Arch. Biochem. **2**:37, 1943.

485. Giordano, A. S.: Idiopathic Hypoprothrombinemia, Am. J. Clin. Path. **13**:285, 1943.

486. Warner, E. D.: Vitamin K Deficiency, M. Clin. North America **27**:371, 1943.

487. Dam, H.: Medical Aspects of Vitamin K, Journal-Lancet **63**:353, 1943.

488. Allen, J. G.: Clinical Experience with a Water Soluble Vitamin K-Like Snbstance (Tetrasodium 2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester), Am. J. M. Sc. **205**:97, 1943.

prothrombin was due to inadequate absorption and in 17 to intrahepatic disease. A maximum therapeutic effect never required more than 5 to 10 mg. per day. Nevertheless 2 normal men were given 200 mg. intravenously in 1 dose without untoward effect. Oral and intramuscular administration was found to result in better sustained levels of prothrombin in patients for whom continued supplement was necessary. One patient was given 8 mg. daily for thirty months without toxic effect.

For Disease of the Liver: Allen [489] reviewed the present status of the use of determination of prothrombin as a test of hepatic function. He concluded from his own extensive study and from the experience of others that its chief use lies in the difficult clinical problem of differentiating between intrahepatic and obstructive jaundice. The physiologic principles involved are important. The production and maintenance by the liver of the normal amount of prothrombin in the circulating blood require that an adequate amount of the fat-soluble vitamin K contained in the diet be absorbed from the gastro-intestinal tract. Bile is essential for the absorption of this vitamin, as for any other fat-soluble substance. Obstructive biliary lesions or external biliary fistula will lead to inadequate absorption of vitamin K and a prothrombin deficiency. It is found practically that this type of prothrombin deficiency responds readily to administration of vitamin K. The fat-soluble compounds when given orally must be given with bile salts, but the latter are unnecessary if the synthetic water-soluble preparations are used or if a parenteral route is chosen. When extensive disease of the hepatic parenchyma results in a low prothrombin level, there is ordinarily little or no response to administration of vitamin K. The prothrombin response to vitamin K may thus offer a practical means of distinguishing between obstructive and other types of jaundice.

This differentiation was made correctly for all but 1 of 98 jaundiced patients in whose cases the test was used. The failure occurred in a patient with long-standing biliary obstruction with hepatitis. Biliary obstruction notoriously leads to hepatic parenchymal damage which may mask the presence of a lesion amenable to surgical treatment. With jaundice of less than two months' duration the prothrombin level was invariably restored to normal by vitamin K. A significant rise in the level was obtained more often than not even when the jaundice was of five to seven months' duration. Hepatitis and cholangitis complicating an obstruction or a pure inflammatory hepatic disorder leads to a poor prothrombin response to vitamin K more rapidly than obstruction alone.

The amount of vitamin K administered for the test should be more than adequate. Eight milligrams or more of the vitamin was usually given every twenty-four hours. The initial level of prothrombin must be 80 per cent or below. A normal or nearly normal prothrombin level is expected in forty-eight hours. A poor rise, less than 25 per cent, indicates intrahepatic disease. Allen regards this test as a most accurate clinical test if the jaundice is of less than six or eight weeks' duration and if the patient is free of cholangitis.

The use of the prothrombin test as a measure of hepatic function otherwise is controversial. In Allen's experience it may be so used if serial determinations are made over a period of time providing an optimal intake of vitamin K is assured. He has found that the trend of the prothrombin level closely parallels the clinical course of the hepatic disease.

A similar study of prothrombin deficiency in biliary obstruction and diseases of the liver was made by Herbert,[490] using the two stage method of Warner, Brinkhaus and Smith for determination of prothrombin. Her findings agree in general with those of other workers. Among 79 patients with obstructive jaundice with serum bilirubin not over 2.4 mg. per hundred cubic centimeters, there were only 3 with prothrombin deficiency. Among the 51 patients with more severe jaundice there were only 16 with normal prothrombin levels. The author found no regular correlation between the serum bilirubin and the prothrombin level or between phosphatase and prothrombin. Among 19 patients with persistent jaundice due to neoplastic obstruction, the prothrombin remained at a normal level as long as four weeks after the onset of jaundice in 8 instances but fell below 50 per cent in 4. In a similar group whose jaundice was of more than four weeks' duration the prothrombin was invariably low, less than 50 per cent of normal in 10 of 14 patients. In the patients with obstructive jaundice treatment with vitamin K regularly caused a rise in the plasma prothrombin. The author preferred to use the water-soluble synthetic preparations given intramuscularly.

Of 53 patients with obstructive jaundice who came to operation only 7 had abnormal postoperative bleeding, and of these 5 had a normal

489. Allen, J. G.: The Diagnostic Value of Prothrombin Response to Vitamin K Therapy as a Means of Differentiating Between Intrahepatic and Obstructive Jaundice, Surg., Gynec. & Obst. **76**:401, 1943.

490. Herbert, F. K.: Prothrombin Deficiency in Biliary Obstruction and Diseases of the Liver, New England J. Med. **229**:265, 1943.

preoperative prothrombin level, but with the onset of bleeding gross prothrombin deficiencies were discovered. It was thus again demonstrated that the prothrombin level may fall postoperatively and that administration of vitamin K should be continued through the operative period. The critical prothrombin level during a period of wound healing appears to be about 60 per cent or lower.

Twenty-seven of 40 patients with diverse types of disease of the liver had deficient plasma prothrombin. Values below 70 per cent of normal, however, were found only in those whose hepatic disease was easily demonstrated by the levulose tolerance test. There was no significant prothrombin response when vitamin K was given to those with primary hepatic disease.

Armentano and Geher [491] report findings in agreement with those just cited as to the rapid response to vitamin K of low prothrombin levels associated with obstructive jaundice. In cardiac decompensation with hepatomegaly there may be a low prothrombin level present, which spontaneously clears with restitution of compensation. They believe that a favorable response to vitamin K in diseases of the liver is a good prognostic omen.

Davis and his associates [492] have found that a single intravenous injection of vitamin K_1 oxide in patients with low prothrombin levels due to a deficient absorption of vitamin K results in a prompt and sustained therapeutic effect. In 1 patient with obstructive jaundice the prothrombin remained normal for eighteen days and in another for ten days. For administration 10 mg. of the oxide dissolved in 3 cc. of alcohol was drawn into a syringe containing 10 cc. of isotonic solution of sodium chloride just before injection.

Tanturi, Bay and Banfi [493] investigated the blood prothrombin level in dogs with experimental biliary obstruction and compared the findings with those encountered in cases of biliary obstruction in human beings. They confirmed the findings of other investigators that chloroform anesthesia and operative procedures involving manipulation of the liver resulted in severe degrees of hypoprothrombinemia which persisted for two to four days before subsiding spontaneously. Dogs in whom the gallbladder was removed and the common bile duct was ligated survived for as long as three to ten months. A special diet with a high meat content was provided, and bile was given as a supplement. In these dogs, the prothrombin returned to normal after the postoperative fall, and there was no further decline during the period of survival. Hemorrhagic tendencies did not appear. The authors believe that the plasma prothrombin level parallels the functional capacity of the liver.

For Hemorrhagic Disease of the Newborn: The discovery by Waddell and associates in 1939 of a striking prolongation in prothrombin and bleeding times in newborn infants which responded to the administration of vitamin K initiated a flood of collateral investigation as to the cause and circumstances of the well known hemorrhagic disease of the newborn. It has now been repeatedly demonstrated that "physiologic" hypoprothrombinemia occurs during the first seven to ten days of life, probably due to the small reserve supply of vitamin K at birth, the negligible amount in the milk and the absence of bacterial synthesis of this vitamin in the intestine. That the hypoprothrombinemia is associated with a hemorrhagic tendency is conceded by most authors. During the past year preventive treatment with vitamin K during the antepartum and early neonatal period has held the focus of attention. Toohey [494] studied 100 infants and found that 20 mg. of synthetic vitamin K given to the mother a few hours before delivery and 5 to 10 mg. given to the infant shortly after birth produced the best results in preventing hypoprothrombinemia. Ballon [495] reported satisfactory results from administering 10 mg. of synthetic vitamin K on the first postpartum day. Fiechter [496] reports that a 20 mg. dose of synthetic vitamin K given to the mother five to ten days ante partum prevented a fall in the infant's prothrombin level. Algner [497] recommends giving vitamin K to both mother and infant in the same doses as advocated by Toohey. He reports cases of intracranial bleeding and melena neonatorum in which prolonged prothrombin times returned to normal with vitamin K therapy and clinical improvement appeared to result. Webster and Fitzgerald [498] present evidence to show

491. Armentano, L., and Geher, F.: Die Verwendung von Vitamin K zur Prüfung der Leberfunktion, Klin. Wchnschr. **21**:425, 1942.

492. Davis, W. A.; Frank, H. A.; Hurwitz, A., and Seligman, A. M.: Intravenous Use of Vitamin K_1 Oxide, Arch. Surg. **46**:296 (Feb.) 1943.

493. Tanturi, C. A.; Bay, R., and Banfi, R. F.: La protrombinemia en la obstrucción biliar experimental y humana, Semana méd. **1**:1357, 1943.

494. Toohey, M.: Vitamin K Requirements of the Newborn, Arch. Dis. Childhood **17**:187, 1942.

495. Ballon, O.: Ueber die Prophylaxe der Hypoprothrombinaemie der Neugeborenen mit Vitamin K, Schweiz. med. Wchnschr. **72**:1119, 1942.

496. Fiechter, N.: Neuere Erfahrungen über die Wirkungsweise von Vitamin K (Synkavit Roche) bie Neugeborenen, Schweiz. med. Wchnschr. **72**:1252, 1942.

497. Algner, A.: Der Prothrombingehalt des Neugeborenen und seine Beeinflussung durch Vitamin K, Wien. klin. Wchnschr. **56**:88, 1943.

498. Webster, A., and Fitzgerald, J. E.: Clinical Use of Vitamin K in Obstetrics, S. Clin. North America **23**:85, 1943.

that the incidence of neonatal hemorrhage is slightly higher in babies born of mothers not treated with vitamin K. They emphasize that many minor hemorrhages are due to birth trauma and have no relation either to vitamin K or to prothrombin. Kaplan and his associates [499] report the case of a newborn infant in whom vitamin K failed to correct hypoprothrombinemia. Autopsy showed a large hepatic infarction with some disturbance of the remaining hepatic tissue.

The outright assumption that hypoprothrombinemia due to lack of vitamin K accounts for all types of bleeding during early life has met with vigorous contradiction and has led to a closer analysis of the clinical phenomena involved. Parmelee [500] gives an excellent discussion of the many types and degrees of neonatal bleeding. There is as yet no uniformity of opinion as to what should be included in the category of hemorrhagic disease of the newborn. Some authors include petechial hemorrhages in the palate, forehead or scalp, subconjunctival and retinal hemorrhages, sternomastoid hematoma, vaginal bleeding and red blood cells in the spinal fluid or urine. Parmelee would exclude all these as well as cerebral hemorrhage, cephalhematoma and "coffee-ground" vomitus from this disease entity. Hemorrhagic disease of the newborn varies in incidence from 1:118 to 1:2,500, according to the criteria adopted in its diagnosis. Before proposed types of therapy can be finally evaluated the disease must be defined and its natural course determined. Most bleeding is mild and will recover spontaneously. Bleeding and coagulation times regularly become prolonged during the first three days of life along with the fall in the level of plasma prothrombin. The latter is corrected or prevented by the administration of vitamin K unless there is a disturbance of hepatic function severe enough to interfere with the synthesis of prothrombin. Many infants have extremely low prothrombin levels without a hemorrhagic tendency becoming manifest. Parmelee believes that factors other than prothrombin deficiency must be considered in neonatal hemorrhage, especially capillary fragility, trauma, asphyxia and lack of vitamin C. He cites the cases of 2 infants with severe melena in whom vitamin K restored a low prothrombin value to normal but bleeding did not stop until transfusions of whole blood were given.

499. Kaplan, L.; Perlstein, M. A., and Hess, E. R.: Infarction of the Liver and Hypoprothrombinemia: Report of Their Association in a Newborn Infant with Failure of Vitamin K Therapy, Am. J. Dis. Child. **65**: 258 (Feb.) 1943.

500. Parmelee, A. H.: Hemorrhagic Disease of the Newborn, J. Michigan M. Soc. **42**:455, 1943.

A similar discussion of the diagnostic problems in neonatal bleeding is given by Scobbie,[501] who reports a clinical study of 146 infants with hemorrhagic disease of the newborn. She notes that recently many types of bleeding formerly excluded have been included in this diagnosis. In 89 per cent of her cases hemorrhage began during the first three days of life, and in 44 per cent it began on the second day of life. One hundred and thirty-five patients had hematemeses or melena or both. The prothrombin index was obtained in 15 infants with hemorrhagic disease, 7 of them being below 40 per cent and 10 below 55 per cent. In a group of normal infants without hemorrhage there were many instances of equally severe hypoprothrombinemia. The response of the prothrombin to vitamin K and to intravenous, subcutaneous and intramuscular injections of blood was studied. The prothrombin level rose rapidly with vitamin K therapy but responded nearly as well to blood transfusion. There was little improvement following subcutaneous or intramuscular injection of blood.

Moloney [502] reports a study interesting in this connection, of the capillary fragility in 55 infants during the first eight days of life. Sixty per cent of these newborn infants were shown to have an unexpectedly low capillary resistance to suction. Of the 55 infants, 9 were graded as having slight, 12 moderately severe, 8 severe and 4 very severe reduction in capillary resistance on the first day of life. A daily improvement was demonstrated until after the fourth day only 16 gave mildly positive reactions. The infants with the greatest capillary fragility on the average had been born after longer and harder labors during which more analgesic and anesthetic drugs had been used.

Effect of Dicoumarin: The physiologic effects of dicoumarin and related compounds continue to be investigated in many laboratories. Lehmann [503] studied the action of coumarin, 4-hydroxycoumarin, 3 methyl-4-hydroxycoumarin, and 3, 3′-methylene-bis-(4-acetoxycoumarin) in rabbits. He found these compounds no more advantageous than the original 3,3′-methylene bis (4-hydroxycoumarin). No active, stable, water-soluble substitute was found. Jansen and Jansen [504] prepared and tested a number of chemi-

501. Scobbie, E. B. S.: Haemorrhagic Disease of the Newborn, Arch. Dis. Childhood **17**:175, 1942.

502. Moloney, W. C.: The Occurrence of Abnormal Capillary Fragility in the Newborn, Am. J. M. Sc. **205**:229, 1943.

503. Lehmann, J.: Effect of Coumarin and Dicoumarin Derivatives on Prothrombin Level, Lancet **1**: 458, 1943.

504. Jansen, K. F., and Jansen, K. A.: Ueber die Konstitutionspecifität der hemorrhagischen Wirkung von 3,3′-Methylene bis (4 Hydroxycoumarin), Ztschr. f. physiol. Chem. **277**:66, 1942

cally related compounds as to their effect in prolonging the prothrombin time. Only 3,3′-ethylene-bis-(4-oxycoumarin) was found to be potent, and this only weakly so.

Richards [505] investigated fever as a factor which may possibly modify the action of dicoumarin. Rats were made febrile by injections of typhoid vaccine or a yeast suspension, and dicoumarin was given while serial observations on the prothrombin time were made. In the presence of fever the prothrombin time was greatly prolonged as compared with that for controls without fever. Richards and Steggerda [506] designed a similar series of experiments to assay the comparative effect of dicoumarin in disease of the liver. Carbon tetrachloride was injected into rats subcutaneously to produce hepatic damage, not severe enough in degree, however, to result in hypoprothrombinemia. In these animals dicoumarin gave an increased and prolonged depression of the prothrombin level as compared with normal animals.

Shapiro, Redish and Campbell [507] investigated the role of disease of the liver in altering the individual response to dicoumarin therapy. The minimal effective dose of dicoumarin for 20 normal persons was found to be 100 mg., as measured by the prolongation of the prothrombin time of 12.5 per cent plasma. Half this dose, 50 mg., was given to 16 persons with hepatic disease. No response was observed in the persons with hepatic disease whose initial prothrombin levels were not depressed. All the persons with initially prolonged prothrombin times responded to the small dose of dicoumarin, somewhat in proportion to the original depression.

In another communication Shapiro and his associates [508] reported a clinical study of the relation of vitamin K to the hypoprothrombinemia induced by dicoumarin. Evidence that the two were related appeared in the early animal experiments of Link and collaborators, who found it necessary to maintain animals on diets low in vitamin K in order to produce the hemorrhagic sweet clover disease with dicoumarin. Clinically no response from the usual doses of vitamin K was ever demonstrated in dicoumarin hypoprothrombinemia. Shapiro and co-workers found that with minimal effective doses of dicoumarin, 100 to 150 mg., the resulting depression of prothrombin could be neutralized by high doses of vitamin K, about 75 mg. a day.

Davidson and MacDonald [509] investigated the effect of vitamin K_1 oxide on the hypoprothrombinemia induced by dicoumarin. Five patients were given single doses of dicoumarin varying from 0.5 to 1.0 Gm. Large doses of vitamin K_1 oxide, 180 to 450 mg., were given both with the dicoumarin and after the hypoprothrombinemia had been produced. In 4 of the 5 patients the depression of prothrombin was prevented or, if established, was reversed. No serious toxic effect from the vitamin K_1 was observed. The effect of this vitamin on hypoprothrombinemia induced by other than single doses of dicoumarin has not been investigated.

During their study of the anticoagulant and hemorrhagic agent dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) in recent years, Link and his collaborators [510] found that the clotting power of blood and plasma was not affected by this chemical in vitro and that no effect occurred in vivo for several hours after oral or intravenous administration. If a single dose was given the anticoagulant largely disappeared from the blood stream before hypoprothrombinemia could be demonstrated. One possible explanation of this mode of action would be that dicoumarin must undergo chemical change in the animal body before prothrombin formation is inhibited or prothrombin in some way inactivated. The quantitative chemical degradation of 3,3′-methylene-bis-(4-hydroxycoumarin) was then determined, and various analogues were tested physiologically. Only those compounds which theoretically might yield salicylic acid or an orthohydroxybenzoic acid derivative on degradation were found to possess anticoagulant activity.

The effect of oral and intravenous administration of salicylic acid in rats maintained on a ration low in vitamin K was then tested. The prothrombin levels were determined by the one stage method with 12.5 per cent plasma. Severe hypoprothrombinemia developed in about twenty days if 100 mg. of salicylic acid was administered

505. Richards, R. K.: Influence of Fever upon the Action of 3,3′-Methylene-Bis-(4-Hydroxycoumarin) Dicoumarol, Science **97**:313, 1943.

506. Richards, R. K., and Steggerda, F. R.: Dicumarol (3,3′-Methylene-Bis-[4-Hydroxycoumarin]), in Rats with Impaired Liver or Kidney Function, Proc. Soc. Exper. Biol. & Med. **52**:358, 1943.

507. Shapiro, S.; Redish, M. H., and Campbell, H. A.: Studies on Prothrombin: The Effects of a Single Small Dose of Dicumarol (3,3′ Methylene-Bis [4-Hydroxycoumarin]) in Liver Disease, Am. J. M. Sc. **205**:808, 1943.

508. Shapiro, S.; Redish, M. H., and Campbell, H. A.: Prothrombin Studies: Effect of Vitamin K upon Hypoprothrombinemia Induced by Dicumarol in Man, Proc. Soc. Exper. Biol. & Med. **52**:12, 1943.

509. Davidson, C. S., and MacDonald, H.: The Effect of Vitamin K_1 Oxide on Hypoprothrombinemia Induced by Dicoumarin, New England J. Med. **229**: 353, 1943.

510. Link, K. P.; Overman, R. S.; Sullivan, W. R.; Huebner, C. F., and Scheel, L. D.: Studies on the Hemorrhagic Sweet Clover Disease: Hypoprothrombinemia in the Rat Induced by Salicylic Acid, J. Biol. Chem. **147**:463, 1943.

in the daily diet. With 300 mg. a day severe hypoprothrombinemia developed in five days and the average survival was but ten days, and there were typical hemorrhagic manifestations resembling the sweet clover disease of cattle. Intravenous doses of 25 to 50 mg. of salicylic acid gave a similar depression of prothrombin. The maximum effect of a single dose of sodium salicylate was realized in twelve hours, with normal prothrombin values being restored within twenty-four hours. There was no hemorrhagic tendency evident following single oral or intravenous doses of the salicylate. The hypoprothrombinemia did not appear after administration of sodium salicylate unless the rats were maintained on a diet low in vitamin K. Addition of synthetic vitamin K to the basic diet prevented its appearance.

Several investigators subsequently verified and extended these observations. Rapoport, Wing and Guest [511] gave dogs intramuscular injections of methyl salicylate but found no resulting alteration in the prothrombin level. When rabbits were given similar treatment severe hypoprothrombinemia developed. This species difference had been noted by Link and his collaborators, who correlated it with the facility with which vitamin K deficiency could be produced in different experimental animals. Rapoport, Wing and Guest studied, in addition, the prothrombin levels in 15 children 6 to 14 years of age who were being given sodium salicylate or acetylsalicylic acid, 1.5 to 8 Gm. daily. With the higher doses, 6 to 8 Gm. daily, the prothrombin level fell to 50 per cent of normal. Meyer and Howard [512] studied the prothrombin levels in 13 patients who were given 5.3 Gm. of acetylsalicylic acid daily for three to eleven days. In nearly all cases the prothrombin level fell to 50 per cent of normal after three or four days of adminstration of the drug, at which time there was some prolongation of the blood coagulation time. After the use of the drug was discontinued for two to four days, normal values returned. Sodium salicylate given in about the same dosage had the same effect. Administration of 6 mg. of synthetic vitamin K daily with the salicylate neither prevented nor corrected the depression of prothrombin. Shapiro and his co-workers [513] confirmed the depression of the prothrombin level by salicylate. When large doses of vitamin K were given, 20 mg. orally and 6 mg. intramuscularly, with a daily dose of 6 Gm. of acetylsalicylic acid, the expected hypoprothrombinemia did not appear. Since vitamin K therapy in the usual clinical dosage has not been found to prevent or reverse the effect of dicoumarin on the prothrombin level or the coagulation time of the blood, there would be little reason to anticipate a different response when the hypoprothrombinemia was due to salicylate. The responses to high doses of the vitamin are similar. The authors found some evidence that dicoumarin and salicylates are cumulative in effect.

The possible clinical implications of these observations were generally appreciated by the investigators cited. Salicylates may prove useful among the drugs given to prevent or treat intravascular thrombosis. It has not been shown, however, that a ponderable clinical danger of hemorrhage exists with ordinary use of salicylates. Coburn [514] has recently reported the use of massive salicylate therapy, 10 to 20 Gm. of sodium salicylate per day given intravenously, in the treatment of acute rheumatic fever. Toxic manifestations were minimal, and there were no hemorrhagic manifestations. The prothrombin time was not prolonged when determined for 6 patients receiving this type of therapy. The possibilities that salicylate depression of the plasma prothrombin might be more significant in patients with some degree of vitamin K deficiency or might predispose to surgical hemorrhage have not yet been explored.

Heparin.—Many practical problems encountered in the use of heparin make the clinical use of this drug difficult. The variability of individual response is one troublesome problem. De Takáts [515] has devised a heparin tolerance test as a helpful guide in therapy. Ten milligrams of heparin is injected intravenously, and the capillary clotting time is measured at ten, twenty, thirty and forty minutes. The clotting time of normal persons lengthens to four and a half to five and a half minutes after a lapse of ten or twenty minutes. In some persons, how-

511. Rapoport, S.; Wing, M., and Guest, G. M.: Hypoprothrombinemia After Salicylate Administration in Man and Rabbits, Proc. Soc. Exper. Biol. & Med. **53**:40, 1943.

512. Meyer, O. O., and Howard, B.: Production of Hypoprothrombinemia and Hypocoagulability of the Blood with Salicylates, Proc. Soc. Exper. Biol. & Med. **53**:234, 1943.

513. Shapiro, S.; Redish, M. H., and Campbell, H. A.: Studies on Prothrombin: The Prothrombinopenic Effect of Salicylate in Man, Proc. Soc. Exper. Biol. & Med. **53**:251, 1943.

514. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever, Bull. Johns Hopkins Hosp. **73**:435, 1943.

515. de Takáts, G.: Heparin Tolerance: A Test of the Clotting Mechanism, Surg., Gynec. & Obst. **77**:31, 1943.

ever, even this small dose produced an exaggerated response, with flushing, dyspnea, choking and faintness. Resistance to heparin likewise is found, most frequently during the first three or four postoperative days, at a time when anticoagulant therapy, if it is to be used, is most needed. The amount of heparin required can be judged by the heparin tolerance curve; persons who have low responses may be given larger doses, and hyperreactors can be protected against the serious effects of overdosage. De Takáts believes also that a low heparin response indicates a liability to venous thrombosis and is itself an indication for anticoagulant therapy as much as a history of previous thromboses, old age, etc.

In treating venous thromboses de Takáts gives heparin for three days with dicoumarin, while awaiting the latter's effect. The dose of dicoumarin employed is 300 mg. at once and 100 mg. daily. Heparin is given in 50 mg. doses every three or four hours day and night.

De Takáts [516] reports also studies of the effect of sulfur compounds on blood clotting as judged by the alteration of the heparin tolerance. Patients were given intravenous injections of 1 Gm. of sodium thiosulfate or sodium tetrathionate, and their response to heparin was tested. Both of these compounds were found to increase the response to heparin. Clinical use of these drugs for patients with Buerger's disease followed this discovery and has been of therapeutic promise. Incidentally, patients taking sulfonamide drugs were also found to react more to the heparin tolerance test than normal persons.

Loewe and Rosenblatt [517] announced in a preliminary report that they have perfected a method for the subcutaneous administration of heparin by which safe anticoagulant therapy may be maintained continuously for two to seven weeks. Rabinovitch and Pines [518] studied the effect of heparin on experimentally produced venous thrombosis. They found that intravascular clots resulting from injury to the wall of a vein could be prevented or reduced in magnitude by preliminary injection of heparin. Quick [433] has previously emphasized that one important effect of heparin in the process of inhibiting coagulation of blood is the prevention of agglutination of platelets. Baronofsky and Quick [519] present further observations on the occurrence of this phenomenon.

Jaques and Waters [520] have continued their work on the identity and origin of the anticoagulant of anaphylactic shock, long suspected to be heparin. By the use of improved methods they succeeded in isolating heparin in crystalline form from the blood of dogs in acute anaphylactic shock. Since heparin could not be isolated from the blood of normal dogs by the same methods, they believe that it is now proved that heparin is actually the anticoagulant of anaphylactic shock.

Seegers and Smith [521] report a study of the quantitative relationships of antithrombic activity in plasma. The capacity of plasma to destroy thrombin was found to depend fundamentally on the heparin co-factor which is present, while the role of heparin is that of a catalyst. An equation was devised to express the quantitative relationship so as to provide an assay for the co-factor, or antithrombin. A study of the same subject was reported by Volkert.[522] He implicates a protein enzyme as a constant component of the heparin co-factor system. Jorpes [523] presents an authoritative review of the intricate chemistry of heparin. He doubts from the work reviewed that heparin has ever been crystallized, but he regards its mucoitin-sulfuric acid chemical structure as definitely established.

Intravascular Clotting and Thrombosis.—The problems associated with the intravascular clotting of blood have been subjected to intensive investigation in recent years. Ochsner and DeBakey,[524] who have made important contributions in this field, discuss the present status of various clinical aspects. They point out that the sequelae of intravenous clotting are of interest to the physician and the patient rather than the thrombus per se. Massive pulmonary embolism, often instantaneously fatal, may result from phlebothrombosis, an incident which itself may give rise to few or no symptoms or signs. The

516. de Takáts, G.: The Effect of Sulfur Compounds on Blood Clotting, Surgery **14**:661, 1943.

517. Loewe, L., and Rosenblatt, P.: A New Method for the Subcutaneous Administration of Heparin, Bull. New York Acad. Med. **19**:657, 1943.

518. Rabinovitch, J., and Pines, B.: The Effect of Heparin on Experimentally Produced Venous Thrombosis, Surgery **14**:669, 1943.

519. Baronofsky, I. D., and Quick, A. J.: Heparin and the Agglutination of Platelets in Vitro, Proc. Soc. Exper. Biol. & Med. **53**:173, 1943.

520. Jaques, L. B., and Waters, E. T.: The Identity and Origin of the Anticoagulant of Anaphylactic Shock in the Dog, J. Physiol. **99**:454, 1941.

521. Seegers, W. H., and Smith, H. P.: Antithrombic Activity of Plasma: Quantitative Interrelationship, Proc. Soc. Exper. Biol. & Med. **52**:159, 1943.

522. Volkert, M.: Der Antithrombingehalt der Blutes und seine Beziehung zum Heparin, Biochem. Ztschr. **314**:34, 1943.

523. Jorpes, J. E.: Sur Chemie des Heparins, Ztschr. f. physiol. Chem. **278**:7, 1943.

524. Ochsner, A., and DeBakey, M.: Intravenous Clotting and Its Sequelae, Surgery **14**:679, 1943.

recognition that massive embolism is preceded by nonfatal pulmonary infarcts in perhaps 75 per cent of these patients opens the way for energetic treatment directed toward isolating the source of the thrombi surgically. Nonsuppurative thrombophlebitis may be followed by postphlebitic edema, infection or ulceration. Suppurative thrombophlebitis may give rise to embolism, pneumonitis, pulmonary abscess or sepsis. The many simple prophylactic measures of proved value in preventing the intravenous clotting of blood under certain predisposing conditions, the technic of phlebography and the principles of surgical treatment are discussed.

Since the two anticoagulants heparin and dicoumarin have been available for clinical trial, many investigations have been undertaken to determine the practicality, indications and results of their use, both prophylactically and in the treatment of intravascular thrombosis. During the past year numerous reports of the clinical use of dicoumarin have appeared. It was employed in many cases in conjunction with heparin.

Rhoads, Walker and Panzer [525] report their experience with both of these drugs. Three hundred milligrams of dicoumarin was given on the first day and 200 mg. on the second, and on the third day the prothrombin level was determined. If the prothrombin time was over ninety seconds, no further medication was given; if it ranged between sixty and ninety seconds, 100 mg. was administered; and if it was below sixty seconds, 200 mg. was used. No toxic manifestations were seen when dicoumarin was given in these amounts. To counteract an excessively prolonged prothrombin time or actual hemorrhage vitamin K therapy was usually noneffective, and blood transfusions were required to correct the hemorrhagic tendency. The question as to whether or not dicoumarin prevents intravascular clotting is not finally answered. These authors found that the coagulation time of venous blood seldom exceeded normal unless the prothrombin level was depressed below 5 per cent as determined by Quick's method, at which point there was danger of spontaneous hemorrhage. Clinical evidence, however, supports the conclusion that dicoumarin therapy does reduce intravascular clotting.

As heparin exerts an effect complementary to that of dicoumarin, a trial of combined therapy with both drugs was suggested. Since heparin acts in plasma both as an antiprothrombin and as an antithrombin, it was thought that a smaller dose should be effective when the prothrombin level had been previously reduced by the use of dicoumarin. It was found that a single intravenous dose of heparin produced an effect on the clotting time lasting twenty-four hours in patients previously treated with dicoumarin. For such patients an intramuscular injection of 5 cc. of heparin every eight to twelve hours usually kept the coagulation time consistently above normal. The most effective anticoagulant therapy is attained, according to the authors, by using both drugs. A basal level of dicoumarin therapy is advised, which is then supplemented by heparin. Excessive heparinization can be counteracted by the administration of protamine. The combined therapy is guided by frequent determinations of the clotting and prothrombin times.

Barker, Allen and Waugh [526] attempted to evaluate the use of dicoumarin in the prevention of postoperative thrombophlebitis and pulmonary embolism. They classified their patients into five groups: (1) those who had had one episode of pulmonary embolism or infarction after operation and had survived; (2) those in whom thrombophlebitis developed postoperatively; (3) those who had had pulmonary embolism or thrombophlebitis with a previous operation or within six months prior to operation; (4) patients recovering from abdominal hysterectomy, and (5) patients with conditions predisposing to intravascular clotting. From an earlier statistical study the expected incidence of thrombophlebitis and pulmonary embolism was fairly well known for each of these groups. Four hundred and ninety-seven patients were given dicoumarin during their immediate postoperative convalescence in doses adequate to secure a definite increase in the prothrombin time. In a few cases heparin was employed when an immediate anticoagulant effect was desired. In all five groups of patients the actual incidence of postoperative venous thrombosis and embolism was far less than the expected. The authors believe, therefore, that dicoumarin is of definite value in preventing these complications. This therapy has an added risk, since 47 patients had abnormal postoperative bleeding, but in only 18 was it severe. One fatal hemorrhage occurred. The authors regard as absolute contraindications to this type of therapy the presence of renal insufficiency, purpura, other hemorrhagic tendency or prothrombin deficiency, and subacute bacterial endocarditis. Relative contraindications include open wounds, the necessity for a fur-

525. Rhoads, J. E.; Walker, J., and Panzer, L.: Control of Blood Coagulability with Coumarin and Other Drugs, Northwest Med. **42**:182, 1943.

526. Barker, N. W.; Allen, E. V., and Waugh, J. M.: The Use of Dicumarol [3,3′ Methylenebis (4-Hydroxycoumarin)] in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **18**:102, 1943.

ther surgical procedure within two weeks and continuous gastric drainage.

A general review of the role of anticoagulants in the prevention of thrombosis appeared as an editorial in the *Lancet*.[527] The trend of experience in many different quarters has been favorable. DeBakey,[528] in an editorial in *Surgery*, discusses this problem. He alleges that simpler, safer and more economical prophylactic agents than anticoagulants are available, the use of which has given better results than have been obtained with anticoagulant therapy. He cites a series of 4,410 consecutive major surgical operations performed at Charity Hospital of New Orleans with only 3 instances of postoperative thrombophlebitis. In another series of 6,000 operations not a single pulmonary embolism occurred. The risk attendant to the use of dicoumarin is emphasized, and the contraindications for its use are recounted.

Davidson and MacDonald[529] studied the action of dicoumarin intensively in a small number of patients. They confirmed other workers' finding that the oral administration of this drug prolongs the prothrombin time and to a less extent the clotting time of whole blood. Persons in their series showed large and unpredictable variations in their response to dicoumarin. A single dose in the amount of 15 mg. per kilogram given to a normal person reduced the prothrombin concentration below 30 per cent for a period of five days, and the prothrombin did not return to normal until five more days had elapsed. The coagulation time, measured in glass and in lusteroid tubes, was extremely variable, but it was usually prolonged, if the prothrombin level was greatly depressed, to the neighborhood of 5 per cent of normal. Plasma from patients receiving dicoumarin was as effective as normal plasma in hastening the coagulation of the blood of hemophiliacs. A number of tests of hepatic function made serially while patients were receiving dicoumarin showed no change. Neither small doses of synthetic vitamin K nor large doses, up to 75 mg., had any effect on severely reduced prothrombin levels, and blood transfusions had either slight or no effect as measured by the prothrombin time. The authors point out the precautions to be observed and the hazards encountered during the clinical use of dicoumarin.

Bingham, Meyer and Howard[530] report further experience with the clinical use of dicoumarin. The proper dose for 80 per cent of their patients was 5 mg. per kilogram initially followed by a daily dose of 1.5 mg. per kilogram. Two patients were given the drug for long periods, eighty-one and ninety-two days, without toxic effects. The ordinary use of anesthetics in dogs did not increase their sensitivity to the action of this drug.

Wasserman and Stats[531] administered dicoumarin to 71 patients with a variety of medical and surgical diseases. The practical management of dicoumarin therapy, the untoward effects and the clinical results are discussed. Lehmann[532] treated 100 patients with venous thrombosis with dicoumarin. Administration of the drug was started at the first sign of thrombosis with a dose of 500 mg. and was repeated with doses of 125 to 250 mg. as indicated by the prothrombin time. For half the patients active movement of the extremities was prescribed. The time of recovery with this plan of treatment ranged from one to three weeks, whereas formerly five to eight weeks was required. The recovery time of the group who practiced active movement was significantly shorter. Thirty-two patients with thrombophlebitis were treated with dicoumarin with beneficial effect. One hundred and seventy of 278 patients recovering from gynecologic laparotomies were given dicoumarin prophylactically starting on the first postoperative day. A definite reduction in the incidence of postoperative thrombosis and pulmonary embolism was obtained. Hemorrhage was the only serious complication encountered, occurring in 9 per cent of the cases. The contraindications to dicoumarin therapy are outlined.

Lam[533] discusses the combined use of heparin and dicoumarin. He gives statistics to show that in patients who have had one nonfatal pulmonary embolus anticoagulant therapy reduces the expected mortality from 11.8 per cent to 3.3 per cent.

527. Dicoumarin for Thrombosis, Lancet **1**:621, 1943.

528. DeBakey, M.: Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis, Surgery **13**:456, 1943.

529. Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3,3′-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**:24, 1943.

530. Bingham, J. B.; Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3′-Methylenebis (4-Hydroxycoumarin): Report on Further Clinical Observations, Am. J. M. Sc. **205**:587, 1943.

531. Wasserman, L. R., and Stats, D.: Clinical Observations on the Effect of 3,3′-Methylenebis (4-Hydroxycoumarin), Am. J. M. Sc. **206**:466, 1943.

532. Lehmann, J.: Thrombosis: Treatment and Prevention with Methylenebis (Hydroxycoumarin), Lancet **1**:611, 1943.

533. Lam, C. R.: The Anti-Coagulants Heparin and Dicoumarol, J. Michigan M. Soc. **42**:968, 1943.

Klien [534] discusses the use of anticoagulant therapy in occlusion of the central vein of the retina, emphasizing the importance of an etiologic diagnosis before such treatment is considered. When the venous thrombosis is due to sclerosis of the vessels in an elderly person or to inflammation of the wall of the vein, as in tuberculous retinal periphlebitis, such therapy is either useless or contraindicated, respectively. Anticoagulants should prove useful in combating diseases of the blood such as polycythemia and primary thrombocythemia or when thrombosis follows venous stasis due to the ischemia of arterial spasm. Adler [535] recommends the combined use of heparin and dicoumarin for thrombosis of the retinal vein.

Luke [536] presents the case of a soldier in whom there developed without known cause symptoms of an acute obstruction of the small intestine. Eight hours after the first symptom and three and a half hours after the onset of severe symptoms, laparotomy was done. Four and one-half feet (1.4 meters) of purplish, edematous and distended but viable jejunum was found. The veins in the edge of the mesentery were thrombosed. The abdomen was closed without resection of the bowel, and treatment with heparin was started. The anticoagulant therapy was continued for ten and one-half days. The patient recovered without complication.

Hirschboeck and Coffey [537] have interested themselves in the clot retraction time as a laboratory procedure of possible value in predicting the likelihood of pulmonary embolism in situations predisposing to intravenous thrombosis. It was thought that strong and rapid clot retraction would favor dislodgment of a thrombus from the wall of a vessel if one were formed. Increase in the blood platelets and in plasma fibrinogen, both known to occur postoperatively, and anemia are all factors which favor rapid clot retraction. The clot retraction time was determined in 10 cases of pulmonary embolism and found to be uniformly shorter than normal. The test may prove of value in indicating the relative urgency of anticoagulant therapy.

534. Klien, B. A.: Anticoagulant Therapy of Occlusion of Central Vein of Retina in Relation to Pathogenesis and Differential Diagnosis, Arch. Ophth. **29**: 699 (May) 1943.

535. Adler, F. H.: Heparin and Dicoumarin, Arch. Ophth. **30**:164 (July) 1943.

536. Luke, J. C.: Mesenteric Venous Thrombosis: Treatment with Heparin, Lancet **1**:552, 1943.

537. Hirschboeck, J. C., and Coffey, W. L.: Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, Am. J. M. Sc. **205**:727, 1943.

Cahan [538] reports the case of a patient who was inadvertently allowed to continue taking dicoumarin in a dosage of 100 mg. per day after an operation until he had consumed 2,800 mg. of the drug. The patient was admitted to another hospital with hemorrhagic and purpuric manifestations. A pronounced prothrombin deficiency and a prolonged bleeding time were discovered. The patient recovered.

Fibrinogen.—Fibrinogen has been the subject of several investigations reported during the past year. Laki [539] describes a method of isolating fibrinogen from the other protein constituents of hog plasma and finally crystallizing it from a dilute phosphate buffer solution in the cold. The fibrinogen was obtained as needle-like crystals arranged in star or network patterns. Chargaff and Bendich [540] continued their studies on the mechanism of coagulation of fibrinogen. A number of synthetic agents were found to coagulate fibrinogen, including two quinone derivatives, ninhydrin and alloxan. Most of the active clotting agents are known to be capable of oxidizing amino acids and certain peptides. The authors suggest that the action of thrombin on fibrinogen may be an analogous oxidative process. Goldfarb and Tarlov [541] introduced a method for determining the tensile strength of clots. A high correlation was found between the tensile strength of a clot and the amount of plasma fibrinogen. A rough quantitative measurement of the latter can be obtained by determining the tensile strength of the clot.

Platelets.—The occurrence of a vasoconstricting substance liberated by disintegrating platelets and its possible role in hemostasis were investigated by Reid.[542] The substance was assayed by its action in producing a contraction of a spiral strip of ox carotid artery. Serum taken from patients with thrombopenic purpura with prolonged bleeding times and greatly reduced platelet counts had but feeble vasoconstrictor power. Platelets from patients with hereditary thrombasthenia did not differ from those of normal persons in vasoconstrictor activity. The author found no conclusive evi-

538. Cahan, A.: Hemorrhage and Purpura Caused by Dicoumarin, New England J. Med. **228**:820, 1943.

539. Laki, K.: Isolierung und Krystallisierung des Fibrinogens aus Schleineblut, Ztschr. f. physiol. Chem. **273**:95, 1942.

540. Chargaff, E., and Bendich, A.: On the Coagulation of Fibrinogen, J. Biol. Chem. **149**:93, 1943.

541. Goldfarb, A. I., and Tarlov, I. M.: Plasma Clot Tensile Strength Measurement: Its Relation to Plasma Fibrinogen, J. Clin. Investigation **22**:183, 1943.

542. Reid, G.: A Preliminary Note on the Relationship of the Blood Platelets to the Mechanism of Hemostasis, M. J. Australia **2**:244, 1943.

dence that capillary constriction during hemostasis resulted from such a vasoconstrictor substance. Varga and Armentano [543] report experiments showing that venous stasis produced by compression of an extremity results in an increase in the red blood cell count and a fall in the platelet count. Maynard and Hollinger [544] found that the number of thrombocytes in the circulating blood diminished in regions of the extremities where there was peripheral vascular disease.

Japa [545] reports an interesting morphologic study of the development of the megakaryocytes as observed by a special "smash" technic, previously reported. Megakaryocyte nuclei were seen to divide by normal mitosis, synchronously, with each having its own spindle mechanism. The nuclei, accordingly, always numbered two, four, eight, sixteen or thirty-two. The maturity of the cells could be judged by the number of nuclei, with degenerating cells usually possessing eight or more nuclei.

Capillary Permeability.—An extensive review and investigation of capillary fragility in human beings in various states of health and disease was made by Franke.[546] The variability encountered in different body regions, in the two sexes and during menstruation is discussed. Subcutaneous injections of histamine led to both local and general increase in capillary fragility. A similar change occurs with thermal burns, sunburn, exposure to ultraviolet rays, carbon monoxide poisoning, lobar pneumonia, diphtheria, typhus, terminal cachectic conditions and general depression of blood formation.

The capillary resistance in different body regions was studied by Abel.[547] An apparatus exerting a measured amount of suction over an accurately timed interval was used. In general the capillary resistance was increased over the distal parts of the extremities and was greater over the arms than over the legs. In areas where the skin was thin and soft the resistance was least. There was no great difference between the capillary fragility in the flexor area of the elbow and that of the mucous membranes.

Lange [548] introduced a fluorescein method for determining capillary permeability. By this technic the dye is seen under ultraviolet rays to escape from the blood stream into the tissues under conditions of increased permeability. Exposure to cold was found to diminish the capillary permeability despite dilatation of the capillaries. The permeability was not increased by elevating the capillary pressure. In patients who had had resections of sympathetic nerves the capillary permeability was increased above normal. Rigdon and Curl,[549] using an intravenous trypan blue method, showed that roentgen irradiation increased the capillary permeability for a short time.

Mertz [550] studied the capillary resistance in a strain of swine suffering from an inherited bleeding disease. Many of the animals were observed to bleed to death from trivial wounds or from spontaneous hemorrhages. The disease is transmitted as a mendelian recessive, and either sex may be a carrier. The bleeders were found to have consistently a greater increase in capillary fragility than the carriers.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION AND NEPHRITIS

A comprehensive monograph dealing with the changes in the blood in pulmonary tuberculosis was published by Muller.[551] The book is based on routine, serial examinations of the blood of over 1,000 patients admitted consecutively to the Rutland State Sanatorium over a period of five years. The author correlates changes in the peripheral blood with the response of the tissues to infection with tubercle bacilli and to injection of tuberculin. In dealing with the behavior of individual cell types in tuberculosis, she accepts the prevalent view that the monocyte is chiefly concerned in tubercle formation as the lymphocyte is in the repair of tuberculous foci, but she emphasizes that the polymorphonuclear neutrophil reacts characteristically in many phases of the disease. An increased percentage of neutrophils was commonly found, even in the

543. Varga, L., and Armentano, L.: Ein Beitrag zur Entstehung der Thrombopenie, Ztschr. f. klin. Med. **142**:501, 1943.

544. Maynard, M. T.-R., and Hollinger, N.: Thrombocyte Deficit: Behavior of Blood Platelets in Diseases of Vascular Stasis of the Extremities, J. A. M. A. **121**:1194 (April 10) 1943.

545. Japa, J.: A Study of the Morphology and Development of the Megakaryocytes, Brit. J. Exper. Path. **24**:73, 1943.

546. Franke, H.: Untersuchungen über die Capillarwanddichte des Menschen in Gesunden und Kranken Tagen, Ztschr. f. klin. Med. **142**:316, 1943.

547. Abel, G.: Ueber Unterschiede der Capillarresistenz an der Korperoberflache, Deutsches Arch. f. klin. Med. **191**:60, 1943.

548. Lange, K.: The Effect of Cold on Capillary Permeability: A Preliminary Report, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **5**:154, 1942.

549. Rigdon, R. H., and Curl, H.: The Effect of Roentgen Irradiation on Capillary Permeability and Inflammation in the Skin of the Rabbit, Am. J. Roentgenol. **49**:250, 1943.

550. Mertz, E. T.: Abnormal Capillary Resistance in Swine Suffering from an Inherited Bleeding Disease, Am. J. Physiol. **138**:137, 1942.

551. Muller, G. L.: Clinical Significance of the Blood in Tuberculosis, London, Oxford University Press, 1943.

absence of fever with normal or low total white cell counts. Neutrophilia was more common in patients with the more advanced stages of the disease but appeared to be related to the activity of the process rather than to the extent of a given lesion. Monocytosis, with a count of 10 to 15 per cent, occurred in 31.2 per cent of the cases, and counts greater than 16 per cent were obtained in 3.7 per cent. An increased number of monocytes in the peripheral blood was usually found only in patients with fever. The percentage of eosinophils was found to be of little prognostic value but was thought to be related to allergic hypersensitivity to the tubercle bacillus.

Although the sedimentation rate has proved of universal value in clinical tuberculosis, little uniformity in methods of determination and recording and in standards of normality has been attained. Muller proposes an adaptation of several methods which she recommends as being uniformly reliable. As the anticoagulant dry potassium oxalate was selected, because of the unaltered sedimentation, convenience and low cost, although heparin was considered to be possibly the ideal anticoagulant. The Wintrobe tube and the Cutler method of computing the rate from the maximum speed of fall were adopted. The rate is recorded in millimeters of fall per minute after correction for hematocrit variation and for the shrinkage of red cells due to the potassium oxalate. By this technic the upper limit of normality was established as 0.3 mm. per minute. Values greater than 0.4 mm. per minute thus are considered pathologic.

Anemia, indicated by a hemoglobin value below 12 Gm. per hundred cubic centimeters, was found in 22.1 per cent of 1,130 patients with pulmonary tuberculosis, but it was rarely more than moderate in degree. The morphologic types were distributed as follows: normocytic, normochromic, 30.4 per cent; normocytic, hypochromic, 25.6 per cent; microcytic, normochromic, 16.4 per cent; microcytic, hypochromic, 15.6 per cent, and macrocytic, 12 per cent. Pernicious anemia was not encountered. Frank iron deficiency anemia often followed repeated hemoptyses. In cases of the hypochromic and microcytic anemias, even when the condition was not due to loss of blood, the administration of iron was frequently beneficial, although in many cases effective antianemia treatment was impossible without reduction of the toxemia of tuberculosis.

No primary abnormality of the blood or tendency to bleeding was found in patients with pulmonary hemorrhages. In 90 per cent of those who did have hemoptyses, a shift in the neutrophils toward immaturity had been previously noted, and in all an elevated sedimentation rate was present, which indicated activity of the tuberculous lesions.

Muller has given critical attention to the value of hematologic data in the clinical management of pulmonary tuberculosis and believes that careful studies of the blood are indispensable. She found that abnormalities of the blood occurred with greater frequency than fever, increased pulse rate or loss of weight, and frequently supplied information not derived from studies of the sputum or roentgen examinations. The clinical course was reflected by changes in the blood picture of many patients who were doing badly before there was roentgen evidence of extension of the tuberculous lesion. The hematologic signs of particular value were an increased sedimentation rate, leukocytosis with an increased percentage of neutrophils, an increase in neutrophils with nonsegmented nuclei, lymphocytopenia and monocytosis. She believes that a better hematologic judgment can be rendered by considering each change separately rather than by cell formulas, such as Medlar's monocyte/lymphocyte ratio. Studies of the blood are of particular value when changes in type or stage of therapy are being considered. Rest in bed should be continued until hematologic as well as clinical and roentgen improvement definitely ends. During rehabilitation abnormalities of the blood may appear or recur to indicate the instability of lesions and the probability of relapse.

Farber and Miller [552] studied the incidence of prothrombinopenia in a group of patients with tuberculosis in order to evaluate the possible relationship of vitamin K deficiency to pulmonary hemorrhage. Moderate degrees of prothrombin deficiency were found in 33 per cent of the patients who had not had pulmonary bleeding and in 53 per cent of those who had had hemoptyses. The latter group tended to have lower prothrombin values, without, however, approaching hemorrhagic levels. The administration of synthetic vitamin K was effective in restoring the prothrombin time to normal in all cases. The authors believe that, since it has not been established that vitamin K either stops pulmonary hemorrhage or influences its course, the only indication for its use lies in the correction of a demonstrated prothrombin deficiency. The prothrombin level reflects in general the clinical and nutritional status of the patient.

552. Farber, J. E., and Miller, D. K.: Nutritional Studies in Tuberculosis, Prothrombin Deficiency and Vitamin K, Am. Rev. Tuberc. **48**:406, 1943.

Paterson [552] reported a study of the prognostic value in tuberculosis of the sedimentation rate, the total white cell count, the Weltman reaction of the serum and the Medlar monocyte/lymphocyte ratio. Thirty patients with different types of tuberculous lesions were followed, and the eventual clinical and roentgenologic outcomes were checked against the earlier results of the blood tests. The prognosis based on the sedimentation rate was 80 per cent accurate, the total white cell count 72.4 per cent, the Weltman reaction 68.5 per cent and the Medlar monocyte/lymphocyte ratio 45 per cent.

An unusual type of febrile illness with leukocytosis and eosinophilia was observed by Weingarten [554] in over 70 patients living in the coastal regions of India. The clinical symptoms began with 1 to 2 degrees (F.) of fever, loss of appetite and loss of weight. Cough, dyspnea and typical evidences of bronchial asthma then appeared, and the spleen became moderately enlarged. Roentgenograms of the chest revealed a generalized, disseminated mottling, especially about the hili and at the bases of the lungs. The roentgen signs usually cleared in about four weeks, although the pulmonary symptoms often lasted longer, in some cases for two to five years. The leukocyte count averaged 20,000 to 40,000 early in the illness, and in 1 case it was 79,000, the increase being due entirely to eosinophils, which increased up to 88 per cent. The cause of the disease was not discovered. All the patients recovered. Neoarsphenamine was an effective and apparently specific therapeutic agent. The author does not think that this disease is the same as Loeffler's syndrome.

Smith [555] reports the case of a patient with Loeffler's syndrome. A 55 year old woman was hospitalized for cough and asthmatic symptoms. She was febrile and had a high leukocyte count, of 20,000, with 49 per cent eosinophils. Roentgenograms of the chest showed an extensive infiltration in the right lung. The pulmonary infiltration cleared in about six weeks, and the blood returned to normal in about three months. Clinically the illness was far less severe than the appearance of the chest indicated.

Pelaez Redondo [556] studied the abnormalities of the blood in 17 soldiers who had contracted kala-azar in Spain. Since most previous investigations had been made on children, the author thought that the studies done on adults were of especial interest. Clinically the irregular fever, chills, splenomegaly and loss of weight might readily suggest the diagnosis of malaria. Although a few investigators have succeeded in isolating the causative organism from the peripheral blood, this has been done so rarely that even with the use of thick drop preparations it cannot be depended on for diagnosis. In most patients with kala-azar a normochromic anemia develops, with a red cell count between 2,000,000 and 3,000,000 per cubic millimeter. The red cells show anisocytosis, poikilocytosis and polychromasia, and nucleated red blood cells are not uncommon. Leukopenia, with a white cell count averaging 1,500 to 3,000, is usually present, and counts as low as 900 were encountered. The white cell count is reduced at the expense of the granulocytes; even agranulocytosis may occur, and a shift toward immaturity is characteristic. Plasma cells may be found in a concentration as high as 3 or 4 per cent. The abnormalities of the peripheral blood, fever and splenomegaly promptly disappear with specific therapy. In this series intravenous injections of calcium antimony tartrate were generally used. It has long been known that Leishman-Donovan bodies are numerous in the bone marrow in kala-azar. Sternal and tibial punctures and splenic punctures have been used frequently in diagnosis. Splenic punctures have not been without hazard. Many authors found that sternal puncture is nearly 100 per cent successful in isolating the organisms of this disease. The procedure gave diagnostically positive results in 11 of the 17 cases in the author's series. The number of Leishman-Donovan bodies varied greatly in different instances, from organisms occurring in every field to only a rare organism being found after a long search. The author describes them as being 2 to 4 microns in diameter, round or oval, having two nuclei of different size and staining violet-red with Giemsa stain. In some cases the organisms were found in clumps and appeared encapsulated. They were also found phagocytosed in white cells. Another feature of the bone marrow in kala-azar is the preponderance of erythroblasts and normoblasts.

Faarup and Ohlsen [557] investigated the anemia of chronic renal disease as related to the histologic picture of the bone marrow. In the expla-

553. Paterson, J. T.: Prognostic Blood Tests in Tuberculosis, Edinburgh M. J. **50**:288, 1943.

554. Weingarten, R. J.: Tropical Eosinophilia, Lancet **1**:103, 1943.

555. Smith, G. H.: Loeffler's Syndrome, South. M. J. **36**:269, 1943.

556. Pelaez Redondo, J.: Die Hämatologie der Kala-Azar der Erwachsenen; diagnostische Bedeutung der Sternalpunktion, Wien. klin. Wchnschr. **55**:585, 1942.

557. Faarup, C., and Ohlsen, S.: Sternalmarkuntersuchungen bei nephrogenen Anämien, Folia haemat. **67**: 152, 1943.

nation of this type of anemia the role of hydremia, renal loss of blood and destruction of blood has been evaluated without finding an adequate cause. The anemia is usually found in late stages of renal disease, but there is no strict correlation between the degree of anemia and the level of retained nitrogen products. A better correlation exists between the degree of anemia and the duration of azotemia. The peripheral blood usually shows little evidence of regeneration, being without anisocytosis, poikilocytosis, nucleated red cells or increase in reticulocytes. This suggests that the anemia is due to diminished production of blood. To investigate this possibility the authors examined the bone marrow obtained by sternal aspiration in 19 patients. A constant finding was hypoplasia of the erythroid elements, a relative increase in myeloid cells sometimes with a shift toward immaturity. In some patients the precursors of red cells were nearly absent. The authors believe that the bone marrow findings confirm the supposition that the anemia is due to decreased blood formation and explain the lack of response to the usual types of antianemia therapy.

CHANGES IN THE BLOOD ASSOCIATED WITH CHEMICAL INTOXICATION

A stippled cell count of 9,000 per million erythrocytes in the absence of other recognizable causes is considered diagnostic of lead intoxication by Sanders.[558] On the other hand, stippled counts as low as 500 per million are compatible with significant lead absorption. Evans and his collaborators[559] found no important differences in the number of stippled cells or the blood values of employees exposed to tetra ethyl lead fumes when one half of the workers were given 100 mg. of ascorbic acid daily for one year. The reticulocyte and the stippled cell count and the degree of polychromatophilia were found by Dressen[560] to be correlated with the atmospheric concentration of lead to which a group of lead battery workers were exposed. Fifteen patients with plumbism were treated effectively by Kety and Letonoff[561] with sodium citrate by mouth, in a dosage of 4 to 5 Gm. three to four times daily. Severe lead colic was promptly relieved in 6 patients after slow intravenous administration of a 2.5 per cent solution of sodium citrate. The lead alloy, solder, administered with the diet, was shown to be without effect on the blood values of dogs or rats by Salomon and Cowgill.[562]

One thousand employees exposed to toluene in atmospheric concentrations of 50 to 1,500 parts per million were studied by Wilson.[563] Ten per cent had symptoms sufficient to make them request medical examination, but in only 1 per cent were there abnormalities in the blood, including anemia, leukopenia, granulocytopenia and thrombopenia. In 2 cases a hypoplastic bone marrow was observed. Toluene, a component of paints, was found by Greenburg and his associates[564] to produce mild anemia, macrocytosis and lymphocytosis when present in 100 to 1,100 parts per million. Leukopenia was not observed in the group of 106 painters studied. Killick and Schilling[565] have concluded that toluene and xylene appear to be the agents responsible for producing lymphocytosis and relative granulocytopenia in persons exposed to the vapors of mixed organic solvents. Browning[566] stresses the importance of a relative lymphocytosis unaccompanied by leukopenia as an early sign of toxic absorption of benzene. Smith[567] reports an instance of fatal aplastic anemia which occurred four years after exposure to benzene in a 49 year old man formerly employed as a rotogravure printer.

Mapharsen given to infants for the treatment of congenital syphilis was found by Astrachan and Cornell[568] to produce a fall in the red cell

558. Sanders, L. W.: Measurement of Industrial Lead Exposure by Determination of Stippling of Erythrocytes, J. Indust. Hyg. & Toxicol. **25**:38, 1943.

559. Evans, E. E.; Norwood, W. D.; Kehoe, R. A., and Machle, W.: The Effects of Ascorbic Acid in Relation to Lead Absorption, J. A. M. A. **121**:501 (Feb. 13) 1943.

560. Dressen, W. C.: The Health of Lead Exposed Storage Battery Workers, J. Indust. Hyg. & Toxicol. **23**:60, 1943.

561. Kety, S. S., and Letonoff, T. V.: The Treatment of Lead Poisoning by Sodium Citrate, Am. J. M. Sc. **205**:406, 1943.

562. Cowgill, G. R., and Salomon, K.: The Possible Toxicity of Lead Alloys: Experiment on the Rat with Solder, J. Indust. Hyg. & Toxicol. **25**:81, 1943. Salomon, K., and Cowgill, G. R.: The Possible Toxicity of Lead Alloy: Experiments on the Dog with Solder, ibid. **25**:91, 1943.

563. Wilson, R. H.: Toluene Poisoning, J. A. M. A. **123**:1106 (Dec. 25) 1943.

564. Greenburg, L.; Mayers, M. R.; Heimann, H., and Moskowitz, S.: Effects of Exposure to Toluene Used as Component of Paints, Indust. Hyg. Bull. **22**: 122, 1943.

565. Killick, E. M., and Schilling, R. S. F.: An Investigation into the Effects of Continued Exposure to the Vapor of Volatile Solvents, J. Indust. Hyg. & Toxicol. **24**:307, 1942.

566. Browning, E.: Toxic Anemia, J. Indust. Hyg. & Toxicol. **25**:124, 1943.

567. Smith, A. R.: Benzol Fatality After Four Years' Freedom from Exposure, Indust. Hyg. Bull. **22**:329, 1943.

568. Astrachan, G. D., and Cornell, V.: Mapharsen in the Treatment of Congenital Syphilis, with Especial Consideration of the Intramuscular Method of Administration, J. A. M. A. **121**:746 (March 6) 1943.

and hemoglobin level. A relatively high dose, 1 mg. per kilogram of body weight, caused an average fall of 620,000 red cells and a drop of 14 per cent in hemoglobin in 5 of 48 persons after an average of eight intramuscular injections.

Chronic trinitrotoluene poisoning produced in rats by Himsworth and Glynn [569] was found to be accompanied by a decline in the hemoglobin level. When the animals were placed on a high fat diet, the fall in iron content of the cells was further increased. An erythroblastic bone marrow was observed, and the spleen contained increased deposits of iron. Alterations in the peripheral blood picture of rats were studied by Dunning and Reich after the subcutaneous injection of carcinogenic hydrocarbons [570] and after the animals were affected with induced and transplanted tumors.[571] A hemolytic microcytic hypochromic anemia followed injections of methylcholanthrene or benzpyrene. Both these carcinogens caused an increase in the number of circulating monocytes, with small doses leading to stimulation and larger amounts to depression of hemopoiesis. Induced and transplanted tumors produced a progressive fall in the red cell and hemoglobin values proportional to the growth of the tumor. Elevated total white cell counts with neutrophilia commonly accompanied the anemia. Ohta,[572] working with rabbits, observed a slower rate of recovery from an artificially induced anemia in animals which harbored transplanted Kato sarcomas. Aspirated marrow showed normal, active erythropoiesis despite the subnormal recovery rate. It was suggested that the presence of the tumor inhibited hemopoiesis not through a direct effect on the bone marrow but rather by altering some physiologic process of the body as a whole. Taylor, McAfee and Taylor [573] report that the hemoglobin level of embryonic Leghorn chicks was found to be depressed by as much as 70 per cent when mammary carcinoma of mice was grown in the yolk sacs. They believe that the decrease in hemoglobin may be explained in part by an inhibitory effect on the liver's role in hemopoiesis.

Carbon monoxide poisoning in dogs produced by inhalation of the gas and by replacement of the animals' blood with erythrocytes previously saturated with carbon monoxide was compared by Drabkin and his associates.[574] More serious disturbances follow poisoning by inhalation, although a level of 75 per cent HbCO was produced in each instance. The difference was explained in part by the far greater partial pressure of the gas to which the tissues were exposed in the inhalation experiments and by the Haldane, Stadie and Martin effect which operated to reduce the available "functional" hemoglobin.

METHODS AND MISCELLANEOUS MATERIAL

The British Research Council's Committee on Traumatic Shock [575] submits a critical report on the current methods for estimating hemoglobin and on the use of the hematocrit. The committee was unable to endorse any colorimetric or photometric method for accurate determinations of hemoglobin. Estimations of iron on washed red cells were recommended as the best available check on determinations of total hemoglobin. The Haldane-Gowers hemoglobinometer, utilizing carbon monoxide, was felt to be the most satisfactory for routine use. The Wintrobe method was recommended for hematocrit determinations. Jenkins and Thomson [576] believe that the spectrophotometer is the only satisfactory instrument for determining hemoglobin, since, once standardized, its permanency, they state, is absolute.

The mean corpuscular hemoglobin, the mean corpuscular hemoglobin concentration and the red cell volume, as determined by the method of Wintrobe, were shown by Lewis and collaborators [577] to follow no definite trend with

569. Himsworth, H. P., and Glynn, L. E.: Experimental Trinitrotoluene Poisoning: Effect of Diet, Clin. Sc. **4**:421, 1942.

570. Dunning, W. F., and Reich, C.: Studies on the Morphology of the Peripheral Blood of Rats: Rats Injected Subcutaneously with Carcinogenic Hydrocarbons, Cancer Research **3**:258, 1943.

571. Dunning, W. F., and Reich, C.: Studies on the Morphology of the Peripheral Blood of Rats: Rats with Induced and Transplanted Tumors, Cancer Research **3**:266, 1943.

572. Ohta, T.: Influence of Malignant Tumors upon the Hematopoietic Organs: Influence of Malignant Tumors upon the Recovery of Artificial Anemia, Far East. Sc. Bull. **2**:17, 1942.

573. Taylor, D. R.; McAfee, M., and Taylor, A.: The Effect of Yolk Sac-Cultivated Tumors on the Hemoglobin Level in the Embryonic Chick, Cancer Research **3**:542, 1943.

574. Drabkin, D. E.; Lewey, F. H.; Bellet, S., and Ehrich, W. H.: The Effect of Replacement of Normal Blood by Erythrocytes Saturated with Carbon Monoxide, Am. J. M. Sc. **205**:755, 1943.

575. Haemoglobinometry and the Use of the Haematocrit: Report to Traumatic Shock Committee of Medical Research Council, Brit. M. J. **1**:209, 1943.

576. Jenkins, C. E., and Thomson, M. L.: Haemoglobinometry and the Use of the Haematocrit, Brit. M. J. **1**:331, 1943.

577. Lewis, R. C.; Kinsman, G. M.; Iliff, A., and Duval, A. M.: Effect of Change of Altitude on Corpuscular Constants of Wintrobe, Am. J. Clin. Path. **13**:208, 1943.

an increase in environmental altitude. This conclusion was reached after a study of 7 persons and supports the contention of Wintrobe that the corpuscular constants provide a universal basis for laboratory diagnosis.

The specific gravity of the serum was determined by the falling drop method of Barbour and Hamilton on the blood of 101 normal adults by Gray and Elliot,[578] who found an average value of 1.0266 ± 0.001, with a range of 1.0242 to 1.0299. In the case of whole blood an average value of 1.0557 ± 0.002 was obtained for a group of 32 normal persons.

A white blood cell–diluting fluid consisting of equal parts of propylene glycol and water is described by Randolph and Gibson.[579] The solution permits accurate enumeration of leukocytes, and when eosin and methylene blue are incorporated, polymorphonuclear, eosinophilic and mononuclear cells may be differentiated in the counting chamber. The greater viscosity of propylene glycol than of the commonly employed 2 per cent acetic acid facilitates accurate filling of the blood-diluting pipet and the counting chamber. Leukocyte counts performed in this medium sixty hours after initial dilution showed no significant variation.

The daily excretion of urobilinogen in the urine and feces in health and disease was studied by Steigmann and Dyniewicz.[580] A total of over 5,000 specimens of urine and over 2,600 of feces were examined by the method of Watson or of Sparkman. Watson's method for the determination of urinary urobilinogen in twenty-four hour specimens was preferred. By this method the normal range of pigment excretion was found to be 3 mg. or less for a twenty-four hour period. Values for fecal urobilinogen obtained by the two methods agreed closely. In the absence of diarrhea or constipation, random specimens of stools yielded urobilinogen values calculated per hundred grams of stool which closely approximated those obtained from a four-day pooled fecal collection. The normal range of fecal urobilinogen estimated from random specimens ranged from 30 to 200 mg. per hundred grams of feces.

The quantitative and qualitative variations in normal leukocytes are reviewed by Sturgis and Bethell.[581] Variations in the total white cell count attributable to observational errors, daily and hourly fluctuations and muscular exertion are discussed. The effects of pregnancy, labor and the puerperium on the leukocyte count are considered, together with variations incident to age and due to starvation and diet, climate, altitude and meteorologic conditions. Donelson, Leichsenring and Ohlson[582] studied 300 healthy college women at intervals of one week to six months and found only a small mean difference between the initial and final erythrocyte, leukocyte and hematocrit values. Britton[583] performed white cell and differential counts on the blood of 552 healthy nurses in a British hospital. The leukocyte counts of 22.6 per cent were less than 5,000 per cubic millimeter. The differential counts, repeated at fortnightly intervals over a two to eight month period, did not vary significantly, and in 29 per cent either fewer granulocytes or fewer lymphocytes were found than the usually accepted minimum normal figures of 3,000 and 1,500 per cubic millimeter respectively. The observed leukopenia was attributed to war conditions of unknown nature.

One hundred subjects 65 years of age or more, divided equally with respect to sex, who were clinically free from disease, were found by Newman and Gitlow[584] to have blood values below those expected for younger adults. These workers obtained average erythrocyte values of 4,420,000 and 4,110,000 per cubic millimeter for males and females respectively. The average hemoglobin value for the males was 12.65 Gm. per hundred cubic centimeters, and the hematocrit value was 41.2 per cent. The females had an average hemoglobin content of 11.7 Gm. per hundred cubic centimeters and a hematocrit value of 36.7 per cent. No deviation from the accepted normal range and no difference between the sexes was encountered in regard to the number of reticulocytes or the resistance of erythrocytes to hypotonic solutions

578. Gray, P. A., and Elliot, A. H.: The Specific Gravity of Whole Blood and Serum, Am. J. M. Sc. **205**:356, 1943.

579. Randolph, T. G., and Gibson, E. B.: Enumeration and Differentiation of Leukocytes in the Counting Chamber with Propylene Glycol-Aqueous Stains, Proc. Soc. Exper. Biol. & Med. **52**:20, 1943.

580. Steigmann, F., and Dyniewicz, J. M.: Studies of Urobilinogen: Daily Urobilinogen Excretion in Urine and Feces in Health and Disease; Evaluation of Watson's and Sparkman's Methods, Gastroenterology **1**:743, 1943.

581. Sturgis, C. C., and Bethell, F. H.: Quantitative and Qualitative Variations in Normal Leucocytes, Physiol. Rev. **23**:279, 1943.

582. Donelson, E. G.; Leichsenring, J. M., and Ohlson, M. A.: Variability of Certain Factors in the Blood Picture of Women, Am. J. Physiol. **138**:626, 1943.

583. Britton, C. J. C.: Serial Leucocyte Counts in Hospital Nurses Not Exposed to Radiation, Lancet **2**:289, 1943.

584. Newman, B., and Gitlow, S.: Blood Studies in the Aged: Erythrocyte in the Aged Male and Female, Am. J. M. Sc. **205**:677, 1943.

of sodium chloride, and similar findings are reported [585] in the case of the total leukocyte and differential counts. Fuks [586] determined the hemoglobin and hematocrit values of 100 Argentine children ranging in age from 2 to 14 years. The blood picture of athletes, as affected by intercollegiate sports, was studied by Farris,[587] who makes an interesting and detailed report. Leukocytosis was produced by all forms of competition. The magnitude of the rise depended on the intensity of the activity rather than on its duration. Unusual fatigue and exhaustion produced a polymorphonuclear response ranging from 80 to 91 per cent of the total white cell count. The erythrocyte values increased somewhat after athletic events of brief duration and decreased after competition which required at least twenty-five minutes.

Baar and Lloyd [588] undertook to determine the daily regeneration rate of human hemoglobin. It was assumed that the enumeration of reticulocytes would serve as a direct measure of the total hemoglobin released daily into the circulation and that no new red cells left the bone marrow under normal conditions except as erythrocytes containing reticulum. Confirmation of the validity of this assumption was obtained in a study of 4 patients in whom no circulating reticulocytes could be found. A fairly close agreement was found between the average excretion of "total bile pigment" in the stool and the average daily fall in circulating hemoglobin. Experimental evidence was sought for an estimate of the reticulocyte maturation time, which yielded a value of seven hours for the average normal reticulated erythrocyte. This is in contrast to the maturation time of two days which is obtained if Riddle's formula is applied to the reticulocyte response in pernicious anemia. If Riddle's formula is corrected by introducing allowances for the coincident and accelerated hemolysis seen in this disease, a maturation time of ten and six-tenths hours is obtained. The normal average reticulocyte percentage of 0.7 and the calculated average maturation time of seven hours allow the estimation of the normal daily rgeneration rate, $\frac{0.7 \times 24}{7}$ hours, or 2.4 per cent. The average life span of an erythrocyte is seen to be $\frac{100}{2.4}$, or forty-two days.

In a second publication Baar [589] studied the velocity of hemoglobin regeneration with his derived formulas in experimental animals made anemic with phenylhydrazine and in human patients in posthemorrhagic stages. Summation curves were constructed for the observed velocity of hemoglobin regeneration. These values proved to conform to the S-shaped curve described by Robertson which characterizes autocatalytic reversible reactions manifested by cellular growth when the nucleus serves as the accelerating agent in tissue multiplication. A further publication on this subject is promised, which will include a collected bibliography.

Leukocytosis-promoting factors have been extracted from inflammatory tissue exudates by Menkin and Kadish.[590] The active principle was found to remain unaltered by storage if first desiccated. The dry purified material produced in dogs an increase of the leukocyte count from an average of 12,973 to 23,365 per cubic millimeter after intracardiac injection. Subcutaneous administration produced a similar response but was delayed in appearance. Methyl acetamide produced a significant leukocytosis in human beings after intramuscular injection according to Zondek and Bromberg.[591] Four patients with typhoid responded similarly, and aspiration of sternal marrow after administration of this material was said to reveal a high percentage of young nonsegmented polymorphonuclear leukocytes. Methyl acetamide combined with parachloroxylenol, a chemotactically inert compound, caused greater and more prolonged leukocytosis. Preliminary results warrant further trial of these compounds, particularly for neutropenic states.

Repeated intravenous injections in rabbits of protagon, an ether-insoluble fraction of lipid extracted from beef brains, was observed to produce a sustained leukocytosis and a myeloid

585. Newman, B., and Gitlow, S.: Blood Studies in the Aged: Leukocytes in the Aged Male and Female, Am. J. M. Sc. **206**:622, 1943.

586. Fuks, D.: Volumen globular, centración globular y hemoglobina en la infancia, Prensa méd. argent. **30**:1313, 1943.

587. Farris, E. J.: The Blood Picture of Athletes as Affected by Intercollegiate Sports, Am. J. Anat. **72**:223, 1943.

588. Baar, H. S., and Lloyd, T. W.: Studies in the Anemias of Infancy and Early Childhood: Regeneration Rate of Haemoglobin and the Life Span of Erythrocytes in Normal and Pathological Conditions, Arch. Dis. Childhood **18**:1, 1943.

589. Baar, H. S.: Studies in Anaemias of Infancy and Early Childhood: Experiments on Blood Regeneration and Their Significance for Life Span of Erythrocytes, Arch. Dis. Childhood **18**:65, 1943.

590. Menkin, V., and Kadish, M. A.: Chemical Fractionation from Exudates of a Factor Promoting Leukocytosis, Am. J. M. Sc. **205**:363, 1943.

591. Zondek, B., and Bromberg, Y. M.: Leukocytosis Induced by Methyl-Acetamide with *p*-Chloro-Xylenol: Chemotactic Effect on Bone Marrow, Am. J. M. Sc. **205**:82, 1943.

hyperplasia of the marrow. Tompkins [592] reports also an increase in the circulating granulocytes and lymphocytes in these animals.

Studies of bone marrow of 10 normal dogs are reported by Meyer and Bloom.[593] The estimated life of the erythrocyte was calculated by Davis [594] as twenty days for the dog and twenty-two days for the rabbit. The values for peripheral blood of 81 dogs, together with observations on bone marrow obtained by puncture from the rib and femur are presented by VanLoon, Clark and Blair.[595] Thirty hamsters were studied by Byrd,[596] and the average red cell, white cell and differential counts and hemoglobin values for these animals were recorded. The average life span of the red cell of the Macacus rhesus monkey was estimated as one hundred days by Harne, Lutz and Davis.[597] Reich and Dunning [598] estimated the hemoglobin and red and white cell values, together with the differential counts, of 2,656 normal rats. This group was made up of animals of seven inbred strains and one hybrid, as well as a miscellaneous group. A significant difference was observed in several of the inbred strains, the hemoglobin ranging from as much as 12.6 Gm. per hundred cubic centimeters of blood to 14.9 Gm. An equal variation was observed in the erythrocyte and leukocyte counts.

Grüneberg [599] gives a detailed account of the anemia occurring in flexed-tailed mice. The siderocyte, a red cell containing considerable amounts of free or easily detachable iron as demonstrated by the prussian blue reaction, is characteristic of this abnormality. One per cent potassium ferrocyanide in 1 per cent hydrochloric acid applied to dried blood films which had been fixed with absolute methyl alcohol revealed small blue-stained granules scattered throughout the cytoplasm of the erythrocytes of these animals. The source of iron in the siderocyte is assumed to be iron which has not been utilized for synthesis of hemoglobin. Siderocytes are present in all stages of development of red cells, although the number of iron-reacting cells is far greater in the "intermediate generation," according to the views of this author. The siderocyte is supposed to disappear in normal and in flex-tailed mice in one and three weeks respectively after birth.

Doniach, Grüneberg and Pearson [600] undertook to examine with the prussian blue reaction the blood films of patients suffering from anemia to see if siderocytes might occur in adult blood under pathologic conditions. It had previously been demonstrated that siderocytes are present in great numbers in the blood of the human embryo and of the adult rat. No siderocytes were found in patients suffering from hypochromic anemia or from pernicious anemia or in 1 patient with hemolytic anemia. In another patient, suffering with Banti's syndrome, who had undergone splenectomy, siderocytes constituted 15.3 per cent of the total erythrocytes. Four other persons were found to have these abnormal cells in the peripheral blood after removal of the spleen, and the phenomenon was also encountered in 2 persons with chronic uremia. The siderocyte is thought to be a sign of an error of iron metabolism, and the stained granule which appears as a distinct blue dot when the blood film is treated with prussian blue is considered to represent iron which has not been utilized for synthesis of hemoglobin. The authors present evidence to suggest that the siderocyte bears no relation to reticulum, reticulocytes, punctate basophilia or Howell-Jolly bodies.

Wislocki [601] confirms the earlier work of Hill indicating that erythropoiesis is present in certain dilated blood vessels of the chorionic villi of the placenta of the marmoset and of other monkeys. Rats on a diet deficient in tryptophan were seen by Albanese and collaborators [602] to have reduced plasma proteins and hemoglobin. Taber, Davis

592. Tompkins, E. H.: The Nucleinate-like Action upon the White Blood Cells of the Ether Insoluble Fraction of Lipoids from Beef Brains, Bull. Johns Hopkins Hosp. **72**:347, 1943.

593. Meyer, L. M., and Bloom, F.: The Bone Marrow of Normal Dogs, Am. J. M. Sc. **206**:637, 1943.

594. Davis, J. E.: Erythrocyte Longevity in Dogs and Rabbits, J. Lab. & Clin. Med. **28**:248, 1943.

595. VanLoon, E. J.; Clark, B. B., and Blair, D.: Hematology of the Peripheral Blood and Bone Marrow of the Dog, J. Lab. & Clin. Med. **28**:1575, 1943.

596. Byrd, J. N.: The Normal Blood Picture of the Hamster, Bull. Creighton Univ. School Med. **2**:5, 1942.

597. Harne, O. G.; Lutz, J. F., and Davis, C. L.: A Preliminary Report of the Blood Picture in the Monkey, with Especial Reference to the Life Duration of the Red Blood Cells, Bull. School Med. Univ. Maryland **28**:39, 1943.

598. Reich, C., and Dunning, W. F.: Studies on the Morphology of the Peripheral Blood of Rats: Normal Rats, Cancer Research **3**:248, 1943.

599. Grüneberg, H.: The Anaemia of Flexed-Tailed Mice (Mus Musculus L.): Siderocytes, J. Genetics **44**:246, 1942.

600. Doniach, I.; Grüneberg, H., and Pearson, J. E. G.: The Occurrence of Siderocytes in Adult Human Blood, J. Path. & Bact. **55**:23, 1943.

601. Wislocki, G. V.: Hemopoiesis in the Chorionic Villi of the Placenta of Platyrrhine Monkeys, Anat. Rec. **85**:349, 1943.

602. Albanese, A. A.; Holt, L. E.; Kajdi, C. N., and Frankston, J. E.: Observations on Tryptophane Deficiency in Rats: Chemical and Morphological Changes in the Blood, J. Biol. Chem. **148**:299, 1943.

and Domm [603] found a rise in the erythrocyte count in fowl receiving testosterone propionate. Other sex hormones produced a decrease. These results are in general agreement with the results reported in dogs, monkeys, and rats receiving various estrogenic substances. A significant difference based on sex was found by Domm, Taber and Davis [604] to exist in the erythrocyte counts of brown Leghorn fowl. The male proved to have higher red cell values than the female and the capon to have a value somewhat lower than that of the male.

The phagocytic activity of rat and mice leukocytes was studied by Cottingham and Mills [605] with various types of deficient diets. Any alteration in the nutritional state of the animal was seen to produce a depression in phagocytic activity. Increased activity of the leukocytes was noted to follow the addition of all vitamins studied with the exception of inositol and paraaminobenzoic acid. Hahn, Bale and Bonner [606] used erythrocytes tagged with radioactive isotopes of iron as a means of determining the amount of blood trapped in the dilated spleen under the influence of sodium pentobarbital. Under sodium pentobarbital anesthesia the spleen was found to weigh four times its weight under other anesthesia, and the engorged organ contained up to 30 per cent of the circulating red cells.

Helpern and Strassman [607] describe a method for differentiation of fetal and adult human hemoglobin. The application of this technic is of medicolegal importance.

The iron content of crystallized human hemoglobin was found to be 0.34 per cent, according to the method used by Bernhardt and Skeggs.[608]

Granick [609] feels that ferritin, a crystalline iron protein present in high concentrations in the spleen, liver and marrow may represent a decomposition product of hemoglobin. Through the use of hydrogen sulfide, which serves in a sensitivity test for the presence of inorganic iron, "gray cells" were demonstrated in the organs where the ferritin content had been shown to be high. It is the author's suggestion that these "gray cells" are degenerating erythrocytes in which the iron and hemoglobin have been set free. This view, if substantiated, would lead to an alternate mechanism for the final destruction of red cells. Instead of the macrophages destroying the erythrocyte, it is proposed that secretions from the sinusoid cells of the spleen may lead to an altered permeability of the erythrocyte, eventual decomposition of heme and release of iron without the necessity of phagocytosis.

Murphy and Green [610] present interesting and in some instances striking photographs of blood films obtained by what they term "profile printing." A blood film from a patient with familial hemolytic jaundice revealed spherocytic erythrocytes which were readily distinguishable from the normal biconcave disks. Interesting illustrations are also presented of hypochromic and sickle cell anemia, pernicious anemia and two forms of leukemia.

Banyai and Cadden [611] discuss in some detail the limits of usefulness of the blood sedimentation rate in the diagnosis of tuberculosis. In 8 per cent of 2,640 patients with active tuberculosis, normal sedimentation rates were encountered. Patients with sputum containing tubercle bacilli were frequently found to have a normal rate. Li [612] used the Cutler method for recording the sedimentation rates of 205 patients with pelvic disease. Sixty-six had malignant tumors, and 97 per cent of these had a rapid sedimentation rate. In the experience of this author a persistently rapid sedimentation rate of blood stored for twenty-four hours did not serve consistently to differentiate malignant from inflammatory processes. The Westergren technic was applied by Tillisch and Habein [613] in 100 cases of benign

603. Taber, E.; Davis, D. E., and Domm, L. V.: Effect of Sex Hormones on the Erythrocyte Number in the Blood of the Domestic Fowl, Am. J. Physiol. **38**:479, 1943.

604. Domm, L. V.; Taber, E., and Davis, D. E.: Comparison of Erythrocyte Numbers in Normal and Hormone-Treated Brown Leghorn Fowl, Proc. Soc. Exper. Biol. & Med. **52**:49, 1943.

605. Cottingham, E., and Mills, C. A.: Influence of Environmental Temperature and Vitamin-Deficiency upon Phagocytic Functions, J. Immunol. **47**:493, 1943.

606. Hahn, P. F.; Bale, W. F., and Bonner, J. F., Jr.: Removal of Red Cells from the Active Circulation by Sodium Pentobarbital, Am. J. Physiol. **138**: 415, 1943.

607. Helpern, M., and Strassman, G.: Differentiation of Fetal and Adult Human Hemoglobin: Its Medicolegal Importance, Especially in Connection with the Alkali Test for Carbon Monoxide in Blood, Arch. Path. **35**:776 (May) 1943.

608. Bernhardt, F. W., and Skeggs, L.: Iron Content of Crystalline Human Hemoglobin, J. Biol. Chem. **147**:19, 1943.

609. Granick, S.: Non-Hematin Iron in Erythrocytes, Proc. Soc. Exper. Biol. & Med. **53**:255, 1943.

610. Murphy, W. P., and Green, E. T.: Profile Printing in the Photomicrography of Blood Cells, Arch. Int. Med. **71**:814 (June) 1943.

611. Banyai, A. L., and Cadden, A. V.: Limitations of the Erythrocyte Sedimentation Test in Tuberculosis, Arch. Int. Med. **72**:245 (Aug.) 1943.

612. Li, K. Y. Y.: The Significance of the Erythrocyte Sedimentation Rate in Pelvic Pathology, Am. J. Obst. & Gynec. **46**:381, 1943.

613. Tillisch, J. H., and Habein, H. C.: Sedimentation Rate in Cases of Benign Hypertrophy and Carcinoma of the Prostate Gland and Carcinoma of the Prostate Gland with Metastasis, J. Urol. **49**:857, 1943.

prostatic hypertrophy and carcinoma of the prostate without and with metastasis. Of the persons with abnormal sedimentation rates, 25 per cent had benign prostatic lesions and 47 per cent had carcinoma. Of the latter group 59 per cent were suffering from a cancer which had metastasized. Apter, Hull and Adams [614] compared the initial sedimentation rate of citrated blood with the rate obtained after twenty-four hours of storage in cases of cancer and of Hodgkin's disease and in cases in which the patients were persons known to be free of such processes. Their results clearly demonstrate that maintenance of the initial sedimentation rate after storage depends in large part on the temperature of the blood when the rate is determined and on the temperature at which the blood is stored. It is concluded that the maintenance of the initial sedimentation rate is not a reliable attribute of cancer and occurs too frequently in blood of persons free from neoplastic processes to serve as a reliable aid in diagnosis. The hospital records of 1,000 consecutive patients were reviewed by Helm,[615] and a prediction was made, based on the history and physical examination, as to the expected sedimentation rate. The observed sedimentation rate ran contrary to the predicted value for 57 patients, but on reanalysis an explanation to account for this discrepancy was found in all but 16 cases. The serum coagulation test devised by Weltmann was used for 80 patients with rheumatic fever over a course of two years of observation by Scherlis and Levy.[616] Simultaneously this group was studied at regular intervals with other laboratory methods commonly used to gage the activity of a rheumatic process. A normal coagulation band and a normal sedimentation rate proved equally reliable in indicating the absence of active disease. In contrast, an abnormal Weltmann reaction was more frequently associated with clinical activity of the disease than was an elevated sedimentation rate. This led to the suggestion that the coagulation band test may serve as a more reliable indicator of the presence of an active process. This view was strengthened by the greater number of abnormally elevated sedimentation rates encountered in the absence of clinically active disease.

614. Apter, L.; Hull, E., and Adams, C. C.: Maintenance of the Sedimentation Rate as a Test for Malignant Disease, Am. J. M. Sc. **206**:169, 1943.

615. Helm, J. D., Jr.: The Predictability of the Character (Increased or Normal) of Erythrocyte Sedimentation Rate: Survey of 1,000 Cases, Am. J. M. Sc. **205**:241, 1943.

616. Scherlis, S., and Levy, D. S.: Comparison of the Value of the Weltmann Reaction and the Erythrocyte Sedimentation Rate in Patients with Rheumatic Heart Disease, Am. Heart J. **26**:355, 1943.

A micrometric apparatus for determining the sedimentation rate of erythrocytes is described by Rogatz.[617] The author found that this method compared favorably with that of Smith and Cutler. Weisz and Taran [618] found that the Cutler micromethod for determining the sedimentation rate proved not only accurate but simple. A comparison of the Cutler and the Westergren method is given by Scott,[619] who feels that the greater technical simplicity of the Cutler method adds to its usefulness. In 92 comparative tests, the Westergren sedimentation rate measured at the end of one hour averaged a 2.48 times greater fall of erythrocytes. It is pointed out that no simple relationship exists between the two methods. A comparison of the Rourke-Ernstene, Wintrobe-Landsberg, Westergren, Linzenmeier and Cutler sedimentation rates as regards technic, and the expected normal range for each method, is available.[620] Reference to the original description is given for each technic.

Bernard [621] compared the fibrinogen and the globulin content and the sedimentation rate of the blood taken from the right and the left side of the heart of rats. The fibrinogen and the globulin content proved higher in the blood from the right side of the heart, and the sedimentation rate was more rapid, in 96 of 100 trials.

An interesting mathematical law is presented by Whittington,[622] which expresses the maximum sedimentation velocity of a given sample of blood. The most important physical variable which required measurement proved to be the "agglutinating power" of the plasma, which was demonstrated as a function of the plasma's viscosity. The effect of plasma proteins on the sedimentation rate of human blood was studied by Gordon and Wardley.[623] The inhibiting ac-

617. Rogatz, J. L.: A Simple Micrometric Apparatus for Determining the Sedimentation Rate of the Erythrocytes, J. Lab. & Clin. Med. **28**:1842, 1943.

618. Weisz, A., and Taran, L. M.: Finger Puncture Method for the Sedimentation Rate, J. Pediat. **22**:565, 1943.

619. Scott, J. M.: A Comparison of the Cutler and Westergren Red Cell Sedimentation Methods, Am. J. Clin. Path. **7**:83, 1943.

620. Technics of Erythrocyte Sedimentation Tests, Queries and Minor Notes, J. A. M. A. **121**:797 (March 6) 1943.

621. Bernard, M.: Die Senkungsgeschwindigkeit der roten Blutkörperchen im Blut der rechten und der linken Herzhälfte, Wien. klin. Wchnschr. **56**:31, 1943.

622. Whittington, R. B.: Blood Sedimentation: A Study in Haemo-Mechanics, Proc. Roy. Soc., London, s.B **131**:183, 1942.

623. Gordon, C. M., and Wardley, J. R.: The Effect of the Plasma Proteins upon the Sedimentation Rate of Human Blood, Biochem. J. **37**:393, 1943.

tion of albumin was found to reside in the globoglycoid fraction. The globulin proved to accelerate the sedimentation rate of red cells, and this effect was traced to the euglobulin fraction. From observations made with varying concentrations of purified proteins it was concluded that the sedimentation rate is controlled not by the absolute concentration of either the total plasma proteins present or any of their fractions but by the inhibition or acceleration of one protein by another. This explanation was offered to account for the failure of others to correlate the sedimentation rate with the concentration of any one given protein fraction. Purified protein fractions were studied by Gray and Mitchell,[624] who found that purified fibrinogen increased the sedimentation rate more effectively than any other protein fraction. Horanyi[625] compared the sedimentation rate of red blood cells in citrated and in native plasma; the latter was kept from clotting by the use of collodion-lined tubes. The sedimentation rate differed for the two plasmas; in general, the citrated plasma yielded more rapid rates. The cause of this discrepancy seemed to be related to the plasma proteins, for in the case of the native plasma the sedimentation rate varied directly with the albumin-globulin ratio. Miki[626] compared the sedimentation rate of citrated plasma with the rate obtained when the erythrocytes were suspended in pleural exudates. A slower fall was observed in the exudate, and the difference from the plasma rate was seen to be increased significantly with critical stages of a patient's illness.

624. Gray, S. J., and Mitchell, E. B.: Effect of Purified Protein Fractions on Sedimentation Rate of Erythrocytes, Proc. Soc. Exper. Biol. & Med. **51**:403, 1943.

625. Horanyi, M.: Die Senkung der roten Blutkörperchen im Nativplasma, Klin. Wchnschr. **22**:359, 1943.

626. Miki, H.: The Sedimentation Rate of the Erythrocytes When Plasma Is Replaced by Various Pathological Body Fluids, Far East. Sc. Bull. **2**:100, 1942.

Book Reviews

The Medical Clinics of North America, New York Number. Vol. 28. Pp. 262. Philadelphia and London: W. B. Saunders Company, 1944.

The New York number of *The Medical Clinics of North America,* is devoted almost entirely to a symposium on psychosomatic medicine, nearly 200 pages of this issue being assigned to a series of articles by fifteen contributors. The symposium deals with a variety of expressions of psychosomatic disease. The choice of subjects is catholic in selection, including such papers as one on the clinical description of psychosomatic medicine, another on neurocirculatory asthenia due to a small heart, another on nonspecific ulcerative colitis and another on stuttering. All of these articles may be read with interest and profit. Psychosomatic medicine is daily of increasing importance, and greater attention is being paid to it, as always happens in periods of war. Certainly the physician of today must realize that innumerable disease entities have a psychic as well as a somatic basis and that the problem of treatment is as much the former as it is the latter.

The last three clinics have to do with miscellaneous subjects. Particularly valuable is the article by Baker, on Rocky Mountain spotted fever.

This New York number of *The Medical Clinics of North America* is unusually good. A careful perusal of its 250 odd pages will yield excellent dividends to the reader.

Surgical Disorders of the Chest. By J. K. Donaldson. Price, $6.50. Pp. 364, with 127 engravings. Philadelphia: Lea & Febiger, 1944.

It is hard for the general physician to view with anything short of despair the increasing number of monographs on special topics, although at the same time he must recognize their value. In the present instance the subject is large enough so that even the 350 odd closely printed pages do hardly more than give a synopsis of the material. The procedures of thoroplasty, for example, are dealt with in ten pages, pulmonary abscess in fifteen and subphrenic abscess in eight. "Something about everything" is, however, to be found, from injuries of the wall of the chest to respiratory physiology to disorders of the esophagus and diaphragmatic hernia. There are many excellent illustrations, references after each chapter and an index. The opinions expressed seem sound, and the book should be useful to both internists and surgeons.

The Electrocardiogram: Its Interpretation and Clinical Application. By Louis H. Sigler, M.D. Price, $7.50. Pp. 415, with 203 illustrations and plates. New York: Grune & Stratton, Inc., 1944.

Many textbooks on electrocardiography are so voluminous that the reader becomes confused at the mere prospect of delving beneath the frontispiece. The author has achieved completeness, relative brevity and simplicity of presentation in this delightful new volume. The smooth, flowing style makes for easy reading. The illustrations are frequent and of good quality. The chapter on interpretation of precordial leads is well illustrated and complete. The source references for material not original are clearly indicated. The book is well indexed. The only criticism offered by the reviewer is that where possible it would seem desirable to adhere completely to the nomenclature set forth by the Criteria Committee of the New York Heart Association rather than to substitute other, though synonomous, terms. This book should prove of especial value to students of electrocardiography.